09/605567

1616

EL385558144US

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this paper and any documents referred to as enclosed or attached are being deposited with the United States Postal Service on this date in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL385558144US addressed to:

Commissioner of Patents
Washington, D.C. 20231
Box: Patent Extension

on 5/11/2001
Date

Bonnie Ferguson
Signature of Person Making Deposit

Bonnie Ferguson
Printed Name of Person Making Deposit

Applicant: Woodward et al

Title: CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS
Allergan Docket: 16955DIVCONCIP(AP)

Enclosed Are:

Certification Under 37 CFR 1.10 (Express Mail Label No. EL385558144US

1. POSTCARD
2. CERTIFICATE OF MAILING BY EXPRESS MAIL
3. TRANSMITTAL LETTER-IN DUPLICATE
4. DECLARATION WITH COPY OF POWER OF ATTORNEY-IN DUPLICATE
5. APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156-IN DUPLICATE
6. EXHIBIT A-1 - IN DUPLICATE
7. ATTACHMENTS A, B, C, D, E, F AND G-IN DUPLICATE

155

#18
Dey
6/16/04

DOCKET NO. 16955DIVCONCIP(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 5,688,819

Issued: November 18, 1997

To: Woodward et al

For: CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS

May 11, 2001

Box Patent Extension
Commissioner of Patents and Trademarks
Washington, D.C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

Sir:

Allergan, a Texas Limited Partnership, (hereinafter "Applicant") hereby submits this application, under 35 U.S.C. §156, for extension of the term of United States Patent No. 5,688,819, by submitting this application pursuant to 37 CFR §1.740.

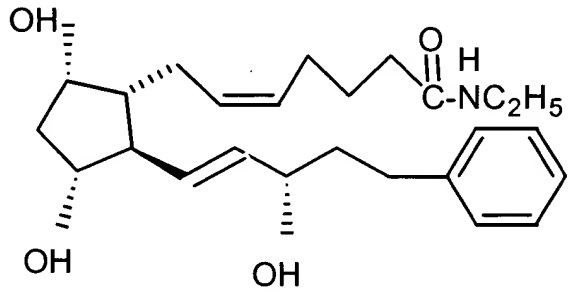
Applicant represents that it is the assignee of the entire interest in and to U.S. Patent No. 5,688,819, by virtue of the following:

U.S. Patent No. 5,688,819 issued on U.S. Patent Application 605,567, which was filed on February 22, 1996, and is a continuation in part of U.S. Patent Application Serial No. 371,339, which was filed on January 11, 1995, and is a continuation of U.S. Patent Application Serial No. 154,244, which was filed on November 18, 1993, now abandoned, and is a divisional of 948,056 filed September 21, 1992, now U.S. Patent 5,352,708.

06/16/2004 AKELLEY 00000027 010885 5688819
01 FC:1457 1120.00 DA

U.S. Patent Application Serial No. 605,567 was assigned by David F. Woodward on April 26, 1996, Steven W. Andrews on May 16, 1996, Robert M. Burk on May 7, 1996 and Michael E. Garst on May 16, 1996 to Allergan, a copy of which assignment is attached as Exhibit A-1.

(1) The approved product (Lumigan®) is a topical formulation of the active ingredient, Bimatoprost, which is cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α]; and, and has the following structure:



Note the package insert for Lumigan® attached hereto as Attachment A.

(2) Lumigan® was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355.

(3) Lumigan® received permission for commercial marketing for use in the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) on March 16, 2001.

(4) The active ingredient of Lumigan®, Bimatoprost, has not previously been approved for commercial marketing under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the sixty (60) day period permitted for submission, the last permitted day for said submission being May 15, 2001.

(6) The complete identification of the patent for which an extension is being sought is as follows:

Inventors:	David F. Woodward; Steven W. Andrews, Robert M. Burk and Michael E. Garst
Patent No.:	5,688,819
Issue Date:	November 18, 1997
Expiration Date:	September 21, 2012

(7) A copy of the patent for which an extension is being sought is attached hereto as "Attachment B".

(8) No disclaimer, or Reexamination Certificate has been issued with respect to U.S. Patent No. 5,688,819. A Certificate of Correction was issued on December 8, 1998, a copy of which is attached hereto as "Attachment C". A copy of the Maintenance Fee Statement indicating payment of the Maintenance Fee, Fourth Year, in May of 2001, is attached hereto as "Attachment D".

(9) U.S. Patent No. 5,688,819 claims the use of the active ingredient of Lumigan®, Bimatoprost, i.e., cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α], as identified in Paragraph (1), above, in a method of treating ocular hypertension or glaucoma. More specifically, claim 10 of this patent cover that compound as follows:

10. The method of claim 9, i.e. treating ocular hypertension or glaucoma, wherein said compound is selected from the group consisting of:

cyclopentane heptenol-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α, 2_β, 3_α, 5_α];

cyclopentane N,N-dimethylheptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α, 2_β, 3_α, 5_α];

cyclopentane N-isopropyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α, 2_β, 3_α, 5_β];

cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α, 2_β, 3_α, 5_β], and

cyclopentane N-methyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_a, 2_b, 3_a, 5_a];

(The italics above are added to specifically point out bimatoprost.)

(10) The relevant dates and information pursuant to 35 § U.S.C. 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review are as set forth in "Attachment E".

(11) A brief description of the activities undertaken by the Applicant during the applicable regulatory review period with respect to Lumigan® and the significant dates applicable to such activities is attached hereto as "Attachment F".

(12) A statement in accordance with 37 CFR § 1.740(a)(12) is attached hereto as "Attachment G".

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon this Application for Extension is to be charged to Applicant's deposit account as authorized in the accompanying letter which is submitted in duplicate.

(15) Any inquiries and/or correspondence relating to this application for patent term extension should be directed to:

Mr. Robert J. Baran
Allergan, Inc.
2525 Dupont Drive
Irvine, California 92612

(16) Applicant's attorney, undersigned, hereby certifies that this application is being submitted in duplicate originals.

(17) The requisite declaration under 37 CFR § 1.740 for extension of patent term under 35 U.S.C. § 156 is also attached hereto.

Respectfully submitted,

ALLERGAN

RJ Baran

Robert J. Baran
Attorney for Applicant
Registration No. 25,806
Telephone: 714/246-4669
Telecopier: 714/246-4249

Allergan
2525 Dupont Drive
Irvine, CA 92612-1599

Express Mail Number EL385558144US Date of Deposit 5/11/2001
I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231

Bonnie Ferguson 5/11/2001

Bonnie Ferguson Date

DOCKET NO. 16955DIVCONCIP(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 5,688,819

Issued: November 18, 1997

May 11, 2001

To: Woodward et al

For: CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS

Box Patent Extension
Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION

Sir:

The undersigned, Attorney for Allergan, which is the applicant for extension of patent term under 35 U.S.C. 156 with respect to U.S. Patent No. 5,688,819, hereby declares that:

(1) He is a patent attorney authorized to practice before the Patent and Trademark Office and has the general authority from the Applicant to act on its behalf in patent matters. (See attached power of attorney.)

(2) He has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. § 156 and 37 CFR § 1.740.

(3) He believes the patent is subject to extension pursuant to 37 CFR § 1.710;

(4) He believes an extension of the length claimed is fully justified under 35 U.S.C. § 156 and the applicable regulations; and

(5) He believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. § 156 and 37 CFR § 1.720.

The undersigned hereby declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Date: May 11, 2001 RJ Baran

Robert J. Baran

Express Mail Number: EL385558144US Date of Deposit 5/11/2001
I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231 on 5/11/2001 (Date)

Bonnie Ferguson Bonnie Ferguson 5/11/2001
Bonnie Ferguson Date

Attorney Docket No. 16955DIV2CIP(AP)

DECLARATION - U.S.A Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled NON-ACIDIC CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application (s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

I hereby appoint Robert Baran, Registration No. 25,806, Martin A. Voet; Registration No. 25,208; and Howard R. Lambert, Registration No. 27,206, as attorneys to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

SEND CORRESPONDENCE TO AND DIRECT TELEPHONE CALLS TO:

Robert J. Baran, Esq.(T2-2E)
ALLERGAN, INC.
Legal Department
2525 Dupont Drive, P.O. Box 19534
Irvine, CA 92713-9534
Telephone: (714)246-4669
Facsimile: (714) 246-4249

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF FIRST INVENTOR:			
First Name: DAVID	Initial F.	Last Name WOODWARD	
RESIDENCE & CITIZENSHIP			
City El Toro	State or Foreign Country California	Country of Citizenship Great Britain	
POST OFFICE ADDRESS			
Post Office Address 23152 Tulip Street	City El Toro	State or Country California	Zip Code 92630
SIGNATURE OF FIRST INVENTOR		DATE: Feb 22 1996	
FULL NAME OF SECOND INVENTOR:			
First Name: STEVEN	Initial W.	Last Name ANDREWS	
RESIDENCE & CITIZENSHIP			
City IRVINE	State or Foreign Country California	Country of Citizenship USA	
POST OFFICE ADDRESS			
Post Office Address 3931 CEDRON ST.	City IRVINE	State or Country California	Zip Code 92714
SIGNATURE OF SECOND INVENTOR		DATE:	
FULL NAME OF THIRD INVENTOR:			
First Name: ROBERT	Initial M.	Last Name BURK	
RESIDENCE & CITIZENSHIP			
City IRVINE	State or Foreign Country California	Country of Citizenship USA	
POST OFFICE ADDRESS			
Post Office Address 1337 CERRITOS DRIVE	City LAGUNA BEACH	State or Country California	Zip Code 92651
SIGNATURE OF THIRD INVENTOR Robert M Burk		DATE: February 22, 1996	
FULL NAME OF FOURTH INVENTOR:			

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF FIRST INVENTOR:			
First Name: DAVID	Initial F.	Last Name WOODWARD	
RESIDENCE & CITIZENSHIP			
City El Toro	State or Foreign Country California	Country of Citizenship Great Britain	
POST OFFICE ADDRESS			
Post Office Address 23152 Tulip Street	City El Toro	State or Country California	Zip Code 92630
SIGNATURE OF FIRST INVENTOR		DATE:	
FULL NAME OF SECOND INVENTOR:			
First Name: STEVEN	Initial W.	Last Name ANDREWS	
RESIDENCE & CITIZENSHIP			
City Rancho Santa Marguerita	State or Foreign Country California	Country of Citizenship USA	
POST OFFICE ADDRESS			
Post Office Address 20 Calle Gazapo St.	City Rancho Santa Marguerita	State or Country California	Zip Code 92688
SIGNATURE OF SECOND INVENTOR Steven W Andrews		DATE: 2/22/96	
FULL NAME OF THIRD INVENTOR:			
First Name: ROBERT	Initial M.	Last Name BURK	
RESIDENCE & CITIZENSHIP			
City IRVINE	State or Foreign Country California	Country of Citizenship USA	
POST OFFICE ADDRESS			
Post Office Address 1337 CERRITOS DRIVE	City LAGUNA BEACH	State or Country California	Zip Code 92651
SIGNATURE OF THIRD INVENTOR		DATE:	
FULL NAME OF FOURTH INVENTOR:			

FULL NAME OF FOURTH INVENTOR:			
First Name: MICHAEL	Initial E.	Last Name GARST	
RESIDENCE & CITIZENSHIP			
City NEWPORT BEACH	State or Foreign Country California	Country of Citizenship USA	
POST OFFICE ADDRESS			
Post Office Address 2627 Raqueta	City NEWPORT BEACH	State or Country California	Zip Code 92660
SIGNATURE OF FOURTH INVENTOR Michael E Garst		DATE: 21 Feb 96	

DOCKET NO. 16955DIVCONCIP(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 5,688,819

Issued: November 18, 1997

To: Woodward et al

For: CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS

May 11, 2001

Box Patent Extension
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Re: Allergan
U.S. Patent No. 5,688,819

Sir:

Transmitted herewith is an application for extension of patent term under 35 U.S.C. 156 with regard to U.S. Patent No. 5,688,819. Two copies are submitted as duplicate originals.

Please charge Deposit Account No. 01-0885 in the amount of $1,120. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Account No. 01-0885. A duplicate of this sheet is enclosed.

Respectfully submitted,

ALLERGAN

By RJ Baran
Robert J. Baran
Attorney for Applicant
Registration No. 25,806

Express Mail Number: EL385558144US Date of Deposit 5/11/2001
I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231 on 5/11/2001 (Date)

Bonnie Ferguson — 5/11/2001
Bonnie Ferguson — Date

EXHIBIT A-1

FORM PTO-1595
1-31-92

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

MAY 11 2001 JC53

Tab settings ▽ ▽ ▽ ▽ ▽ ▽ ▽

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

David F. Woodward
Steven W. Andrews
Robert M. Burk
Michael E. Garst

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: Allergan

Internal Address:

Street Address: 8301 Mars Drive

City: Waco State: TX ZIP: 76712

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other

Execution Date: 4/26/96;5/16/96;5/7/96;5/16/96

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

08/605,567

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Robert J. Baran (T2-2E)
Allergan, Inc.

Internal Address:

Street Address: 2525 Dupont Drive

City: Irvine State: CA ZIP: 92715

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41):..... $ 40.00

☐ Enclosed

☒ Authorized to be charged to deposit account

8. Deposit account number:
01-0885

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Robert J. Baran — Name of Person Signing

RJBaran — Signature

5/20/96 — Date

16955DIV2CIP

Total number of pages comprising cover sheet: 4

OMB No. 0651-0011 (exp. 4/94)

CERTIFICATE OF MAILING

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST-CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231 ON 5/20/96.

RJBaran
Attorney for Applicant

5/20/96
Date

EXHIBIT A

IND 48-929 Correspondence

FDA Correspondence Received	Allergan Application/ Response Sent	Brief Description
N/A Oct 6, 1995 (L)	Sep 28, 1995 N/A	IND Submission FDA received application on Sep 29, 1995
N/A	Sep 28, 1995	Electronic file of IND
N/A	Sep 20, 1996	New Protocol 192024-002
N/A	Nov 11, 1996	Annual Report Information Amendment: Pharmacology Studies – BIO-96-096, BIO-96-099 & BIO-96-112 Toxicology Studies – 1893-3137-7, GP95BN52.503003 & G95BN52.702005
N/A N/A	Aug 28, 1997 Sep 2, 1997	New Protocol 192024-004 Protocol Amendment 192024-004 (Added IRB Approval & Patient Information and Consent Form for specific investigator)
N/A	Oct 6, 1997	CMC Amendment (Stability Data)
N/A	Oct 28, 1997	New Protocol 192024-006
N/A	Nov 11, 1997	Annual Report Pharmacokinetic Studies – PK-96-014, PK-96-020, PK-97-013, PK 97-032, PK-97-036, PK-97-026 & PK-97-023
N/A N/A Apr 30, 1998 (M) N/A N/A Feb 23, 1999 (F)	Feb 13, 1998 Apr 9, 1998 N/A Sep 22, 1998 Dec 8, 1998 Mar 23, 1999	Request for End of Phase 2 Meeting (Apr 20 was proposed) End of Phase 2 Meeting Briefing Package End of Phase 2 Meeting (minutes provided June 4, 1999) Phase 3 Protocol Review (EOP2 commitment) New Protocols: 192024-008 & 192024-009 Response to FDA Comments re: 3-month mouse study reviewed at EOP2 meeting
N/A	Mar 30, 1998	New Protocol 192024-003
N/A	Jun 10, 1998	New Protocol 192024-007
N/A	Jul 13, 1998	New Protocol 192024-005

IND 48-929 Correspondence

FDA Correspondence Received	Allergan Application/ Response Sent	Brief Description
N/A	Sep 11, 1998	Carcinogenicity Waiver Request
Nov 5, 1998 (T)	Nov 16, 1998	Carcinogenicity Waiver Request – Additional Data requested by Lori Gorski and Andrea Weir Nov 5, 1998
Nov 24, 1998 (T)		(Note: Minutes of Nov 24 T-con sent to FDA Jan 8, 1999)
Dec 8, 1998 (F)	N/A	Response to Allergan's question re: 6-Month IV Study in Monkey
N/A	Dec 22, 1998	Review of Protocols for Carcinogenicity Studies
Jan 20, 1999 (P)	Jan 21, 1999	Allergan's response to FDA's request for additional information
N/A	Mar 1, 1999 (T)	Carcinogenicity Studies Timeline
N/A	Mar 29, 1999	Additional Information – EMEA's opinion/waiver granted
N/A	Jun 11, 1999	Proposal to decrease duration of toxicology study
July 15, 1999 (E)	N/A	Acceptance of the Jun 11, 1999 proposal
N/A	Aug 14, 2000	Carcinogenicity Waiver Request for NDA 21-275 Toxicology Study ALG 056 Interim Study Summaries – ALG 053 and ALG 058
Sep 1, 2000 (E)	N/A	Waiver Granted
N/A	Sep 17, 1998	Request for End of Phase 2 CMC Meeting (Nov 12 was proposed)
Oct 28, 1998 (P)	Oct 28, 1998	End of Phase 2 CMC Briefing Package for Nov 17, 1998 meeting (Note: Minutes of meeting sent to FDA Jan 8, 1999)
N/A	Sep 28, 1998	Final Clinical Study Reports: 192024-001 & 192024-002
N/A	Feb 19, 1999	Annual Report Final Clinical Study Report 192024-004 Pharmacokinetics Studies – PK-98-003, PK-98-037, PK-98-035, PK-98-036, ALG 040/982507 and ALG 041/982508 Toxicology Studies – TX98014, ALG 050/983734, 1801-013P and 1801-018 Pharmacology Studies – BIO-98-264, BIO-98-273 and BIO-98-277
Apr 26, 1999 (T)	N/A	FDA had no information at Apr 1999 t-con.
Aug 13, 1999 (E)	Nov 19, 1999	Clinical Pharmacokinetics: Response to Aug 13, 1999 e-mail from Dennis Bashaw to Joanne Holmes Pharmacokinetics Reports – PK-99-121 and PK 99-113
N/A	Aug 18, 1999	Request for Feedback on Clinical Pharmacokinetics Devel. Plan
N/A	Sep 9, 1999	Request Review of Statistical Plan for Phase 3 Studies 008 & 009
Sep 15, 1999 (T)	N/A	FDA Schedules teleconference
N/A	Sep 15, 1999	Request Review of Statistical Plan for Phase 3 Studies 501 & 502
N/A	Oct 6, 1999 (T)	Phase 3 Statistical Plan Discussions
Nov 10, 1999 (E)	N/A	FDA accepted plan for 501 & 502
Jan 11, 2000 (E)	N/A	FDA accepted plan for 008 & 009
N/A	May 14, 1999	Revised Protocol 192024-003 to allow previous use of latanoprost

P = Phone F = Facsimile L = Letter T = Teleconference E = E-mail M = Meeting

IND 48-929 Correspondence

FDA Correspondence Received	Allergan Application/ Response Sent	Brief Description
N/A Jun 22, 1999 (F) Sep 7, 1999 (F) Nov 10, 1999 (E)	May 14, 1999 Aug 11, 1999 Oct 15, 1999 N/A	New Protocols: 192024-501 & 192024-502 FDA comments Additional comments Final comments
N/A	Jun 22, 1999	Final Clinical Study Reports 192024-005 & 192024-007
N/A Aug 17, 1999 (E) Sep 21, 1999 (F)	Jul 16, 1999 Aug 19, 1999 N/A	New Protocols: 192024-010 & 192024-012 Discussions re: 192024-010
N/A	Aug 3, 1999	Toxicology Report TX98004
N/A Aug 16, 1999 (E) N/A Feb 5, 2001 (E)	Mar 30, 1999 N/A Aug 19, 1999 N/A	Pre-clearance of Miragan tradename Miragan tradename rejected Pre-clearance of Lumigan tradename FDA accepted name
N/A	Dec 29, 1999	Safety Report – Initial 15-Day ADR
N/A	Dec 29, 1999	Annual Report Information Amendment: Toxicology Reports – TX97002, TX97003, TX97004, TX97009, TX97015, TX97016, TX97033, TX97034, TX97035 and TX98025 Pharmacokinetic Reports – PK-978-126, PK-99-023, ALG/045, PK-99-037, PK-99045, PK-99-047 and PK-99-100 Pharmacology Reports – BIO-99-298, BIO-99-299, BIO-99-307, BIO-99-308, BIO-99-309, IO-99-311, BIO-99-312, BIO-99-314, BIO-99-315 and BIO-99-318
N/A Feb 8, 2000 (F)	Dec 29, 1999 May 25, 2000	New Protocols – 192024-011, 192024-013 and 192024-014
N/A N/A N/A Mar 22, 2000 (P) Apr 4, 2000 (P) N/A	Feb 1, 2000 Mar 9, 2000 Mar 14, 2000 Mar 27, 2000 Apr 6, 2000 May 24, 2000	Request for Clinical Pre-NDA Meeting (Type B) (Note: requested for March 27 or March 28) Request for CMC Pre-NDA Meeting (Type B) Clinical Pre-NDA Briefing Package CMC Pre-NDA Briefing Package FDA scheduled combined Clinical/CMC meeting for Apr 12, 2000 Supplemental CMC Data requested by FDA Summary of Pre-NDA Meeting of Apr 12, 2000
N/A	Feb 17, 2000	Pharmacology Studies – BIO-99-313, BIO-99323, BIO-99324, BIO-99-326, BIO-00-327, BIO-00-330 and BIO-00-331
N/A	Feb 25, 2000	Safety Report – Initial 15-Day ADR

IND 48-929 Correspondence

FDA Correspondence Received	Allergan Application/ Response Sent	Brief Description
N/A	May 18, 2000	Pharmacology Report BIO-00-329 Clinical Study Report 192024-011 Revised Protocol 192024-014 to extend study duration
N/A	May 22, 2000	Safety Report – Initial 15-Day ADR
N/A	Jun 27, 2000	New Protocol 192024-015
N/A Aug 25, 2000 (F)	Aug 4, 2000	New Protocol 192024-016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FDA Concep
DS
JF
CB
EB
RF
Del FDA Con

IND 48,929

Date OCT 6 1995

Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 48,929

Sponsor: Allergan, Inc.

Name of Drug: AGN 192024 Topical Ophthalmic Solution

Date of Submission: September 28, 1995

Date of Receipt: September 29, 1995

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-520)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact Ms. Kennerly Chapman at (301)594-0301

Sincerely yours,

Kennerly Chapman

for/ Supervisory Consumer Safety Officer
Division of ~~Anti-Infective~~ Drug Products Topical
Office of Drug Evaluation
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-520 - yellow
HFD-520/CSO - green

IND ACKNOWLEDGEMENT

ALLERGAN PHARMACEUTICALS MEMORANDUM
FDA TELEPHONE CONVERSATIONS

FDA Courtesy

X **Telephone**

Date: October 28, 1998 **IND/NDA:** 48,929

To: S. Buxbaum

From: C. Brissey

Subject: Hypotensive Lipids End of Phase 2 Meeting with the FDA 17 Nov 98

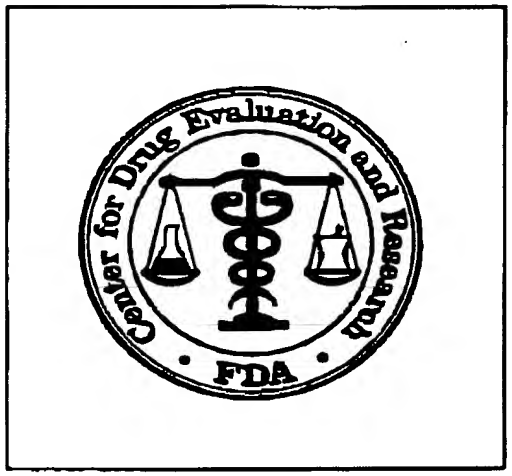
Name of Person(s) Contacted: Raphael Rodriguez

Raphael Rodriguez called to inform us that he must receive the End of Phase 2 Hypotensive Lipids (IND 48,929) briefing packages by Friday, October 30, 1998, or the FDA may need to cancel the November 17, 1998 meeting. Most reviewers will be attending the AAO meeting next week, and it would not be fair to give them only one week to review the package if they did not receive their desk copy until November 9,1998. Some reviewers will want to take the briefing package with them next week for review.

He wants 14 desk copies addressed to his attention, two copies for the Document Room, and the disc that should include the questions to be discussed. He wants to send the questions electronically to the reviewers.

The second alternative for this end of Phase 2 meeting to discuss the CMC section of Hypotensive Lipids could be a teleconference. He is willing to set this up if we decide it is what we want.

FACSIMILE TRANSMISSION RECORD



From: Lori M. Gorski, Project Manager

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Hypotensive Lipid

Date: 12/8/98

FDA Corresp.
SB
SnM

To:
Name Steve Burbaum
Company _____
City _____ State ____
Phone _____

FAX # 714-246-4272

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Steve

Here is a comment from Andrea Weir to follow up on on t-con of 11/24/98 for IND 48,929.

Lori Gorski

RECEIVED

DEC 08 1998

ALLERGAN PHARMACEUTICALS
REGULATORY AFFAIRS

Pharmacology/Toxicology Comments to the Sponsor
IND 48,929
Allergan
December 3, 1998

During the November 24, 1998 teleconference, you asked if the Division felt that the planned 6-month intravenous monkey should be conducted. The answer to this question depends in part on the systemic exposure (relative to clinical systemic exposure) that will be achieved during the 1-year ocular monkey study. If possible please provide us with any available toxicokinetic data for the 1-year monkey study. It is recognized that this study is ongoing, and findings are preliminary.

FDA Corresp.
BALB

HIL
SM, LD

COVER SHEET

FAX

To: Stephen Buxbaum

Allergan, Inc.

Fax #: 714-246-4272

Subject: Meeting Minutes

Date: February 22, 1999 **Re: IND 48,929**

Pages: 5, including this cover sheet.

COMMENTS:

I am faxing you minutes of the meeting of the FDA Center for Drug Evaluation and Research, Executive Carcinogenesis Assessment Committee. Further correspondence will come from the review division.

RECEIVED

FEB 22 1999

ALLERGAN PHARMACEUTICALS
REGULATORY AFFAIRS

From the desk of...

Adele S. Seifried, M.S.
Science Policy Analyst
Pharmacology/Toxicology Staff, HFD-24
1451 Rockville Pike, Woodmont II, Suite 6016
Rockville, MD 20852

301-594-5447
Fax: 301-594-5298

Executive CAC
February 16, 1999

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Glenna Fitzgerald, Ph.D., HFD-120, Alternate Member
Andrea Weir, Ph.D., Team Leader
Zhou Chen, Ph.D., Presenting Reviewer

Author of Draft: Zhou Chen

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND 48,929
Drug Name: **AGN 192024 topical ophthalmic solution (0.03%)**
Sponsor: **Allergan, Inc.**

Background:

AGN 192024 is a structural analog of prostaglandin $F_{2\alpha}$. The drug is under development by Allergan as an ophthalmic formulation for the treatment of glaucoma. AGN 192024 was negative in a battery of in vivo and vitro genotoxicity studies. Clinical studies indicated that the expected human exposure at therapeutic dose was 0.096 ng•hr/ml.

Dose Selection for Mouse Study

The sponsor proposed a 2-year oral gavage study with doses of 0.3, 1.0 and 2.0 mg/kg in both male and female mice based on a pharmacokinetic endpoint in accordance with ICH guidelines. The doses were selected based on a completed 3-month oral gavage study and a 2-week PK study (see tables below). At the proposed high dose (2.0 mg/kg/day) the systemic exposure in mice (6.3 ng•hr/ml) was 200 times of the anticipated therapeutic AUC in humans (0.096 ng•hr/ml). In protein binding study, the unbound fractions of AGN 192024 were 28% and 9% in mouse and human plasma, respectively. The plasma half-life of the drug in mouse (0.54 hr) and human (0.8 hr) were similar. In both species under the clinical dose (human) and proposed high dose (2.0 mg/kg/day in mice), the active metabolite, AGN 191522, was undetectable. Regarding the toxicities shown in the 3-month study, no treatment-related mortality, clinical signs, body weight and food consumption changes, and ophthalmoscopic findings were observed. Histopathology examinations showed increased incidence of medullary lymphoid proliferation in female thymus at 8 or 16 mg/kg/day, and increased incidence of acute inflammatory cells in the superficial layers of the vagina for females at 16 mg/kg/day. Thymus changes were fully recovered. The changes in the vagina were partially recovered during the 4-week recovery period. One female animal receiving the drug at 16 mg/kg/day showed extensive deposits of lymphoma throughout many organs.

A pulmonary adenoma was detected in 1 male from 16 mg/kg/day after recovery period. It was noted that there was no metabolism data available for the mouse. There was discussion concerning the evidence of the lymphoid tissue as a target organ for toxicological effects and the possible of it being a potential carcinogenic target site.

Comparison of PK parameters of AGN 192024

	Mouse	Human
Dose (mg/kg/day)	2.0 (6)	0.0005 (60 kg human) (0.0185)
Cmax (ng/ml)	5.36	0.0822
Metabolite 191522 (blood)	< BLQ (< 0.25 ng/ml)	Not detectable (BLQ = 0.05 ng/ml)
Unbound protein	28%	9%
Plasma t1/2	0.544 hr	0.8 hr
AUC (ng-hr)/ml	6.27	0.096
AUC ratio (animal/human)	203.2	

Comparison of nonclinical exposure and clinical exposure of AGN 192024

Nonclinical dose		Nonclinical exposure		Clinical exposure	Nonclinical/clinical exposure
		Cmax	AUC		
mg/kg/day	mg/m^2/day	(ng/ml)	(ng-hr/ml)	ng-hr/ml	
0.1	0.3	0.366		0.096	
0.3	0.9	1.21		0.096	
1.0	3.0	2.09		0.096	
2.0	6.0	5.36	6.27	0.096	203.2
4.0	12.0	11	6	0.096	194.4
8.0	24.0	16	19	0.096	615.7
16.0	48.0	64	52	0.096	1685.2

Plasma protein binding in mouse is 72%, in human is 91%.

Dose Selection for Rat Study

The sponsor proposed a 2-year oral gavage study with doses of 0.1, 0.3 and 1.0 mg/kg in both male and female rats based on a pharmacokinetic endpoint in accordance with ICH guidelines. The dose selection was based on the PK data obtained from two 3-month oral toxicity study (see tables below). The systemic exposure at the proposed high dose (1.0 mg/kg/day) was 3.8 ng•hr/ml, which was 163 times of the anticipated therapeutic AUC in humans (0.096 ng•hr/ml). In in vitro protein binding study, the unbound fractions of AGN 192024 were 37% and 9% in rat and human plasma, respectively. The plasma half-life of the drug in rat (0.78 hr) and human (0.8 hr) were similar. The liver metabolic profiles across species tested (rat, dog, monkey and man) were similar. LCMS data indicated that in liver slices of rat and man, AGN 192024 was deaminated and glucuronidated. In toxicity studies, a decrease in body weight gain (7-24%) was noted in animals receiving ≥ 4 mg/kg/day of AGN 192024. An increase in serum ALT and AST activities (2- to 5-fold) was observed in male rats at 8 or 16 mg/kg/day. Vacuolated corpora lutea were observed in the female animals at the doses ≥ 0.3 mg/kg/day. An increase in total number of corpora lutea and ovarian weight was also noted in these animals. A dose-response relationship was observed in the ovarian changes. The mechanisms of the ovarian changes were not known, but the sponsor interpreted these changes as pharmacologically related delayed regression of corpora lutea, which resulted in increased number and size of corpora lutea and increased ovarian weight.

Comparison of PK parameters of AGN 192024

	Rat	Human
Dose (mg/kg/day)	1.0	0.0005 (60 kg human)
Cmax (ng/ml)	3.7	0.0822
Metabolite 191522 (blood)	< BLQ (< 0.25 ng/ml)	Not detectable (BLQ = 0.05 ng/ml)
Unbound protein	37%	9%
Plasma t1/2	0.776 hr	0.8 hr
AUC (ng-hr)/ml	3.8	0.096
AUC ratio (animal/human)	162.7	

Comparison of nonclinical exposure and clinical exposure of AGN 192024

Nonclinical dose		Nonclinical exposure		Clinical exposure	Nonclinical/clinical exposure
		Cmax	AUC		
mg/kg/day	mg/m²/day	(ng/ml)	(ng-hr/ml)	ng-hr/ml	
0.1	0.6	0.21		0.096	
0.3	1.8	0.69	0.95	0.096	40.7
1.0	6.0	3.7	3.8	0.096	162.7
4.0	24	39	48	0.096	2855.6
8.0	48	48	81	0.096	3468.8
16.0	96	152	176	0.096	7537.0

Plasma protein binding in mouse is 63%, in human is 91%.

Executive CAC Recommendations and Conclusions:

1. The committee offered concurrence on the proposed doses of 0.3, 1.0, and 2.0 mg/kg for the study in mice contingent upon the sponsor demonstrating similar metabolic profiles for the drug in human and mouse. This may be accomplished through the use of in vitro studies.

2. The committee concurred with the sponsor's proposed doses of 0.1, 0.3, and 1.0 mg/kg for the rat study.

3. The sponsor should consider conducting histopathological examination in all dose groups. The sponsor is reminded that if they plan to conduct the histopathological evaluation of tissues from only the control and high dose animals, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances: (a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups, (b) for an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group, (c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level, or (d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

2/22/99

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\

/Division File, HFD-550
/ChenZ, Presenting Reviewer
/Weir, Team Leader
/ASeifried, Project Manager, HFD-024

Hypotensive Lipids
192024

IND 48,929

Please refer to **Study 043/974324: Toxicity study by oral gavage administration to CD-1 mice for 13 weeks followed by a 4-week recovery period.**

Lymphoma and lymphoid proliferation are not considered typical findings for a 3-month study. Please provide the normal background incidence for these findings and pulmonary adenoma in CD-1 mice of the same age as in your 3-month study. Also, please provide your opinion regarding the significance of these findings.

Thanks.

FDA CORRESP
SB
SM

ATTN: S. BUXBAUM

FR: Z. CHEN
FDA

FAXED
~~FEB 23 1999~~ MLL

RECEIVED
FEB 23 1999
ALLERGAN PHARMACEUTICALS
REGULATORY AFFAIRS

3 FDA Corresp

ALLERGAN

REGULATORY AFFAIRS

INTEROFFICE MEMORANDUM

TO: List

FROM: S. Buxbaum

SUBJECT: Telecon with FDA: Memantine Phase 3 Protocol; Brimonidine/Timolol Efficacy Standards; AGN 192024 Carcinogenicity Study Filing Timing

DATE: March 15, 1999

COPIES: A. Aswad, A. Batoosingh, G. Beck, B. Brar, J. Cheetham, K. Chen, J. Gibson, L. Kaplan, P. Kresel, H-P. Pfleger, A. Rosenthal, J. Wang M. Beekman, G. Cook, U. Junghanns, C. Pugh

---

A telecon with FDA took place on March 1, 1999. Representing Allergan were Steve Buxbaum, Janet Cheetham, Kuankuan Chen and Chris Brissey. Representing FDA were:

Wiley Chambers	Deputy Director
William Boyd	Medical Reviewer
Joanne Holmes	Medical Reviewer
Lori Gorski	Project Management
Raphael Rodriguez	Project Management

1. Memantine Phase 3 Protocol

The revised protocol was mailed to FDA on February 24. FDA brought up the following issues:

a. Glaucoma-change-probability analysis

They had questions (originally conveyed on February 26) about the appropriateness and reproducibility of this analysis. The following documentation was faxed to them on February 26 and March 1:

Letter to CPMP, C. Pugh to I. Moulon, CPMP Scientific Advice – Memantine, January 16, 1998.
Bengtsson B et al. Acta Ophthalmol Scand 1997: 75: 184-188.
Chauhan B et al. Arch Ophthalmol 1999; 117: 24-33.

We informed the Agency that we were redefining our definition of progression based on some modeling done by Chris Johnson on a glaucomatous visual field database. The original definition of 3 points and Pattern-Deviation resulted in inadequate sensitivity and specificity, therefore having a moderate number of false-positives (for glaucomatous progression). Patients with low-to-moderate defects at baseline could have changes detected. However, patients with moderate-to-severe defects could not have changes detected. Chris adopted the methodology used by Chauhan, et al, where 4 points must be replicated for significant change based on Total Deviation; this resulted in more consistent detection of progression in patients with low-to-moderate defects vs. moderate–to-severe defects.

Dr. Chambers was uncomfortable with the $p \leq 0.05$ level because of the inherent variability in the visual fields and multiple locations of individual points. He preferred the $p \leq 0.01$ and 3 location points.
(NOTE: following the teleconference, we got clarification from Chris Johnson that the STATPAC 2 analysis was unable to calculate the significance at anything but the $p \leq 0.05$ level.)

b. Interim analysis

Dr. Chambers said that the final analysis could not be at the $p \leq 0.05$ level. We explained that we used the methods for group-sequential trial by Peto, where the first two analyses are at the $p \leq 0.001$ level, and the final (#3) analysis is at the $p \leq 0.05$ level. Dr. Chambers wanted to read the references for this.

c. Multiple comparisons

Dr. Chambers said that if either dose of memantine (10 mg or 20 mg) could win, then the significance level should be at $p \leq 0.025$ for each active comparison to placebo. We explained that we will use Fisher's protected LSD procedure to test the among-group first; if significant, then pair-wise comparison will be performed.

Post-telecon note:

In response to this discussion, on March 2, 1999, we submitted revisions to key pages of the protocol and included the following additional literature references:

Heijl A, Lindgren A, Lindgren A, et al. Extended empirical statistical package for evaluation of single and multiple fields: Statpak 2. In Mille, RP, Heijl, A. Perimetry Update 1990-1991, New York: Kugler and Ghedini, 303-315.

Milliken GA, Johnson DE. Simultaneous inference procedures and multiple comparisons; in: Analysis of Messy Data, Volume 1: Designed Experiments. Van Nostrand Reinhold, New York, 1984, 33.

Pocock SJ, Geller NL. Interim analyses in randomized clinical trials. Drug Information Journal, 1986, 20: 263-269.

Heijl A, Lindgren, A, Lindgren G, Patella M. Inter-test threshold variability in glaucoma—Importance of censored observation and general field status. Perimetry Update 1990/1991; 189-192.

Chauhan BC. Johnson CA. Test-retest variability of frequency-doubling perimetery and conventional perimetry in glaucoma patients and normal subjects. Invest Ophthalmol Vis Sci 1999 (in press).

2. Brimonidine/timolol efficacy standards

We sought clarification on FDA's expectation for results with the combination product compared to the individual products. As a general rule, the combination has to be better than each individual product at most time points. Potentially, it might not be better at some early stage in drug administration; this would need to be reflected in the labeling. Reference was made to CoSopt results, and Dr. Chambers stated that he would apply the same standards to us as he did to the Merck product.

3. AGN 192024 carcinogenicity study reports – timing of filing

Dr Chambers asserted that as long as we were making a good faith effort, that the studies were ongoing and we intended to submit the results, he would not hold up submission of the NDA if final reports were not available at our scheduled filing date.

FDA corresp:
Brimo pediatric
AGN 192024
memantine
SB

ALLERGAN

REGULATORY AFFAIRS

INTEROFFICE MEMORANDUM

TO: List

FROM: S. Buxbaum

SUBJECT: Telecon with FDA, April 26, 1999: Brimonidine Pediatric, AGN 192024 Clinical Pharmacokinetics, Investigational Labeling, Memantine Phase 3 Protocol

DATE: May 5, 1999

COPIES: A. Aswad, A. Batoosingh, G. Beck, J. Cheetham, K. Chen, M. Cherukury, J. Injejikian, P. Kresel, A. Rosenthal, D. Tang-Liu, A. VanDenburgh

---

A telecon was held with the FDA on April 26, 1999, to discuss outstanding issues on a number of products. Allergan was represented by S. Buxbaum, J. Cheetham, M. Cherukury, D. Tang-Liu and A. VanDenburgh. Present in the room as observers were G. Beck, J. Injejikian and S. Martin. The FDA was represented by W. Chambers, B. Boyd and J. Holmes.

1. Brimonidine pediatric

Allergan needs to send a letter to FDA requesting that they issue us a written request (to conduct studies with brimonidine in the pediatric population). [**Post-telecon note:** The letter of request was sent to FDA on April 30, 1999.] They will issue a request for what they want/expect to have done, e.g., studies in children ages 2 to 16 years old. We have the choice to conduct this as one or more studies. (In fact, we mentioned that our strategy would be to perform a study first in children 7 to 16 years old, followed by another in children in the 2 to 6 year range.) The FDA will provide a date by which they feel the study(ies) should be completed. If this date is past the expiration of our period of exclusivity, there is obviously no need to proceed. In our letter, we need to give at least a general idea of an appropriate study design: X number of patients will be treated for Y period of time, with parameters Z1, Z2 etc. being measured. It is possible to amend the written request up until the time by which the study should be completed.

FDA recognizes that it is unlikely that we could treat children as young as 2 years with the current marketed brimonidine formulation. If we develop a second formulation to treat this population, they will issue a second written request. However, this will necessitate the submission of a new NDA. Approval of the NDA would make us eligible for 3 years marketing exclusivity + 6 months pediatric extension.

2. AGN 192024 clinical pharmacokinetics

Prior to this telecon, the synopses from the three completed PK studies had been faxed to the FDA. We also informed them that we planned on conducting an elderly vs. young study, and that at this time these four studies represented what we felt would be adequate for our NDA filing.

Dr. Chambers indicated that their clinical pharmacologist (Dennis Bashaw) had not had a chance to look over the study synopses, and therefore they were unwilling at this time to offer an opinion.

ACTION: S. Buxbaum will follow up at an appropriate time.

3. Investigational labeling

As the wording in the CFR was formulated to cover studies done both within the US and abroad, we should use the cautionary statement exactly as written: "Caution: New Drug – Limited by Federal (or United States) law to investigational use."

4. Memantine phase 3 protocol

a. Following discontinued subjects

We presented an argument against following subjects discontinued from drug for anything other than ocular changes, since there are so many confounding factors for subjects with their condition and in their age group. However, since we would be including data from subjects taken off drug in the ITT analysis, Dr. Chambers felt that it makes sense to generate real data, i.e., do all the measurements specified in the protocol for subjects in the study. This would serve as a balance and make the numbers more equal (i.e., we could compare results from patients on placebo to those who were discontinued).

Dr. Chambers only wants serious and unexpected AEs reported within 10 working days (this used to be designated "15 days"). It is therefore important that we list all observed AEs in the CIB/labeling so that they will be considered "expected" and therefore not reportable in 10 days.

b. Significance of observed changes

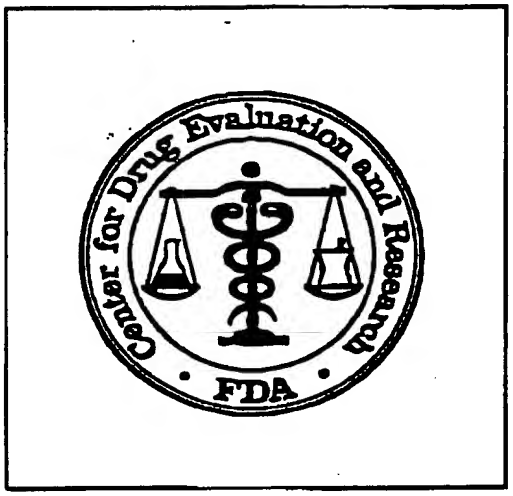
We discussed the definition of visual field defect changes, adjustment for interim analyses and among vs between analysis methods. FDA feels that, ***at this time***, changes using 4 points and a level of 0.05 are not clinically significant. They would consider "much larger changes" to be significant under these circumstances. Nevertheless, the study can proceed. These parameters might prove to be significant after we generate more data.

c. Statistical analyses

Dr. Chambers reiterated that if we do interim analyses, we will need to take a hit on the p-value. Dr. Chambers was more concerned about the final (48-month) p-value, in that it was still 0.05, and he did not feel that this is appropriate. (The protocol takes the "hit" at the 24 and 36 month analyses.) Dr. Chambers suggested that we re-read our references; we told him that we would get back to him on this, since our statistician was not present at this teleconference.

For the question of the among vs between analysis, Dr. Chambers said that the methods proposed in the protocol were appropriate; however, he wanted to point out that if we do only pairwise testings when the among-differences are significant, that we may miss a significant difference. Should we choose to do the pairwise testings first, of course we would have to adjust the p-value for multiple comparisons.

FACSIMILE TRANSMISSION RECORD



From: RAPHAEL RODRIGUEZ

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

Phone 301-827-2040
Fax 301-827-2531

Date: 6-22-99

To:
Name ~~ELIZABETH BANCROFT~~ Steve BaxBaum
Company ALLERGAN
City _____ State CA
Phone # (714) 246-4391

FDA Corresp.
SB
SM
3 extra

FAX # _____

Number of Pages (INCLUDING COVER PAGE) ____

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Additional message:

RE: IND 48,929 AGN 192024

ELIZABETH,

FORWARDING COMMENTS / DEFICIENCY FROM THE MEDICAL REVIEWER.

RAPHAEL

Deficiency/Problem List for Protocol 192024-502-00:

Names and qualifications of investigators should be submitted to the IND as they become available.

The specific beta-blocker utilized can vary among subjects although its regimen may remain constant.

Cardiac and pulmonary exclusions are included because of the adjunctive use of beta-blockers in the study design. This means the study medication may not be adequately evaluated for safety and efficacy in these populations in this particular protocol.

Disagree with sponsor's plan to establish equivalence. To establish equivalence between the groups, a 95% confidence interval should be obtained with the majority of data points showing less than 1 mmHg difference and all data points showing less than 1.5 mmHg difference.

All tests should be two tailed. It is equally important to know whether the test product is better or worse than a control agent.

Informed consent (Section 6 Study Procedures) states "for some subjects, a photograph of your eye(s) ...will be taken at Visit 2, 6, 7, 8, 9, and at your final study visit." According to the protocol, each subject's eye will be photographed. Sponsor should clarify in consent that all subjects would be photographed.

The study medication and vehicle contain benzalkonium chloride. Subjects wearing contact lenses should be advised to wait 5-15 minutes after drop installation before inserting contacts.

HTL FDA Corresp.

Buxbaum_Stephen

From: Raphael Rodriguez 301-827-2090 FAX 301-827-2531 [RODRIGUEZR@cder.fda.gov]
Sent: Thursday, July 15, 1999 4:56 AM
To: Buxbaum_Stephen; 'Rodriguez, Raphael'
Cc: Zhou Chen
Subject: Re: Confirmation of termination of AGN 192024 tox study

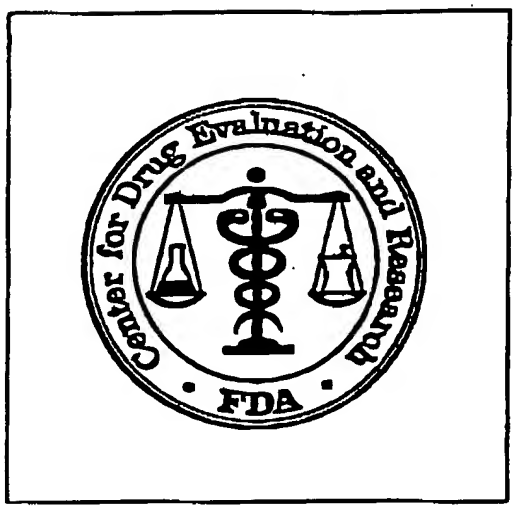
Sensitivity: Confidential

Steve,
My apology for not sending this comment from the pharmacologist earlier.

IND 48,929 SERIAL#030 Terminate the 6 month IV toxicity study in monkeys at 3 months. With respect to the IV study in monkeys, the pharmacologist has no objection to changing the 6 month study into 3 month study.

FDA
AGN 192024
· gm, SB,
LD,

FACSIMILE TRANSMISSION RECORD



From: Raphael R. Rodriguez

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

Phone: (301) 827-2090
Fax: (301) 827-2531

Date: 9/21/99

To:
Name: STEVE
Company: ALLERGAN
City _____ State ____
Phone # _____
FAX # _____

RECEIVED
SEP 22 1999
ALLERGAN PHARMACEUTICALS OPERATIONS GROUP

Number of Pages (INCLUDING COVER PAGE) __

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Additional message:

IND 48,929 AGN 192024
Attn: Steve Buxbaum
From: Raphael R Rodriguez

Reviewer's Comments/Problem List for Protocol 192024-010-00:

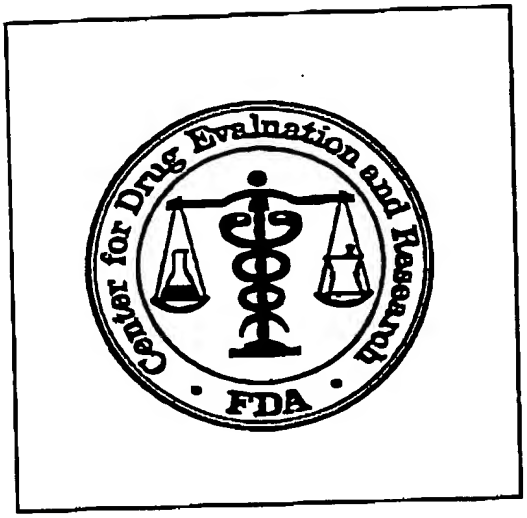
Disagree with Sponsor's response to deficiency issues e-mailed to the Sponsor on August 17, 1999.

Medical Officer's Review of IND 48,929 Amendment 32 is unchanged.

The protocol and analysis plan are insufficient to establish safety and efficacy of the drug product and insufficient to support any advertising claims.

FACSIMILE TRANSMISSION RECORD

FDA-CORRESP.
SB



From: Raphael R. Rodriguez

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

Phone: (301) 827-2090
Fax: (301) 827-2531

Date: 9/7/99

RECEIVED
SEP 07 1999
ALLERGAN PHARMACEUTICALS
REGULATORY AFFAIRS

To:
Name: STEVE BUXBAUM
Company: ALLERGAN
City _____ State ____
Phone # _____
FAX # _____

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Additional message:

RE: IND 48,929 AMENDMENT #34
AGN 19 2024

STEVE,
FORWARDING COMMENTS FROM THE MEDICAL OFFICER.

RAPHAEL

Submitted is a response to deficiency issues faxed to the Sponsor on June 22, 1999 regarding Protocol 192024-502-00.

Reviewer's Comments/Problem List for Protocols 192024-501-00 and -502-00:

1) With the exception of the Medical Officer's comments regarding benzalkonium and contact lenses, the deficiency list was identical for Protocols 192024-501-00 and 192024-502-00 (both were submitted in Amendment 29 on 5/14/99). These comments are applicable to both protocols.

2) Disagree with the sponsor's plan to establish equivalence. When comparing two different regimens with the same drug (i.e., QD vs. BID), the selection of 2 mm Hg as the maximum difference for establishing non-inferiority of HTL once-daily with respect to HTL twice-daily is not acceptable.

Whether comparing drug product to an active control or comparing two different regimens of the same drug, a 95% confidence interval should be obtained with the majority of data points showing less than 1 mm Hg difference and all data points showing less than 1.5 mm Hg difference.

3) Disagree with the sponsor's response to requirements in the protocols for ocular photography. Both protocols indicate that all subjects will be photographed.

In both Protocols 192024-501-00 and 192024-502-00, Section 8.3 states, "... Iris color assessment by gross examination will be performed at all sites. In addition, ocular photography will be performed to collect further data on iris color. The iris color assessment and Polaroid photos will be performed on Day 0 and Week 12."

Attachment 13.1 in both protocols states, "...Changes in iris color pigmentation will be assessed by comparing follow-up photographs with those from baseline."

Please identify the section of the protocol where photography is stated to be optional.

If patients are to be permitted to decide whether they wish to undergo ocular photography and gross examination alone is used, the sponsor may not be able to adequately demonstrate to the agency that the drug product does not cause ocular pigmentary changes. This would be reflected in the drug product's label.

FDA COURTESY.

Buxbaum_Stephen

From: Raphael Rodriguez 301-827-2090 FAX 301-827-2531 [RODRIGUEZR@cder.fda.gov]
Sent: Wednesday, November 10, 1999 1:15 PM
To: Buxbaum_Stephen
Cc: Raphael Rodriguez
Subject: Re: Hypotensive Lipids IND 48,929: follow up

Sensitivity: Confidential

Steve:

1. The clinical development plan is acceptable, provided,
- The to-be marketed formulation has been used in the pharmacokinetic studies
- The treatment regimen is the same as the to-be marketed treatment regimen
- Adequate analytical validation reports have been submitted along with the studies at the time of NDA filing.

2. Tradename "Lumigan" still under review.

3. African-American phase 3 studies is acceptable.

>Raphael,
>
>There are several outstanding issues whose status I would like to discuss
>with you:
>
>1. Acceptability of the clinical PK development plan
>
> On August 18, 1999 (serial 035) we submitted a formal request for
>feedback on our clinical PK development plan. Has this review been
>completed?
>
>2. Acceptability of a tradename
>
> On August 19, 1999 (serial 037) we asked that you consult the
>Nomenclature Committee on the acceptability of the tradename "Lumigan." We
>recognize that any comments you make now would not be binding until the time
>we actually submit the NDA, but your feedback on our proposed tradename
>"Miragan" was very helpful.
>
>3. Number of African-American patients in our phase 3 studies
>
> I have been informed by our Clinical Research department that blacks
>represent 17% average of the enrolled subjects in the two monotherapy
>studies, and 6% in the adjunctive therapy studies, for an overall average of
>13% in the four phase 3 studies. Is this an acceptable racial
>representation? We had anticipated that we could enroll more blacks at the
>South African sites for study 192024-501, but the patient pool has not

been
>able to meet entry criteria.
>
>Thank you for your assistance.
>
>Steve Buxbaum
>Allergan
>(714) 246-4534

FDA Corresp.

Buxbaum_Stephen

From: Joanne Holmes 301-827-2090 FAX 301-827-2531 [HOLMESJ@cder.fda.gov]
Sent: Tuesday, January 11, 2000 10:43 AM
To: Buxbaum_Stephen
Subject: Re: Hypotensive Lipids IND 48,929 Follow up

Sensitivity: Confidential

Steve,

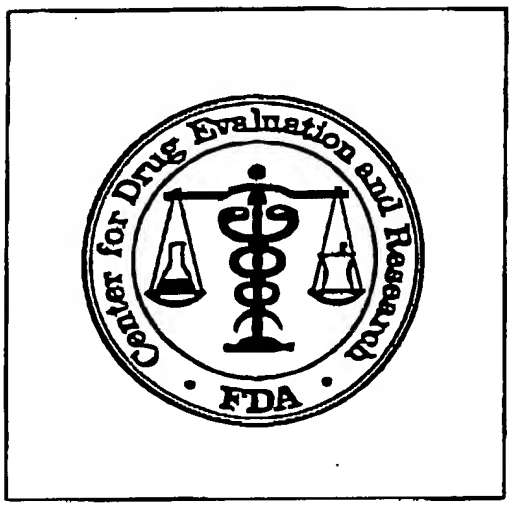
Wiley has looked over the stat plan for IND 48,929 (SN 043, 11/18/99). No objections.

As for the waiver, we would grant a waiver at the time of the NDA submission. You would include a waiver request in the NDA.

We have started looking at the pediatric study for brimonidine. Bill's review is with Wiley, and I believe he has has some comments. We'll pass them on when finalized.

Joanne

FACSIMILE TRANSMISSION RECORD



From: Raphael R. Rodriguez

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

Phone: (301) 827-2090
Fax: (301) 827-2531

FDA CORRESP.
SB
SM

Date: 2/8/2000

To:
Name: STEVE
Company: ALLERGAN
City _____ State CA
Phone # _____
FAX # _____

RECEIVED
FEB 08 2000
ALLERGAN PHARMACEUTICALS
REGULATORY AFFAIRS

Number of Pages (INCLUDING COVER PAGE) __

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Additional message:

RE: IND 48,929

FORWARDING COMMENTS OF THE MEDICAL REVIEWER.

RAPHAEL

February 8, 2000

IND 48,929 AGN 192024 topical ophthalmic solution
ATTN: Stephen Buxbaum
From: Raphael R. Rodriguez

Deficiency/Problem List for Protocols 192024-013 and 192024-014:

1) *Cardiac and pulmonary exclusions are included because of the adjunctive use of beta-blockers in the study design. This means the study medication may not be adequately evaluated for safety and efficacy in these populations in this particular protocol.*

2) *Disagree with sponsor's plan to establish equivalence. Whether comparing drug product to an active control or comparing two different regimens of the same drug, a 95% confidence interval should be obtained with the majority of data points showing less than 1 mm Hg difference and all data points showing less than 1.5 mm Hg difference.*

3) *The choice of a 3-mm Hg difference as a response measure is acceptable for purposes of planning the study. The agency does not necessarily agree that a 3-mm Hg mean decrease in IOP from baseline is a clinically significant difference.*

FACSIMILE TRANSMISSION RECORD

From: **Mike Puglisi, Project Manager**

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2522
Fax 301-827-2531

Date Aug. 25, 2000

To:
Name Stephen Buxbaum
Company Allergan
City _____ State ____
Phone _____

FAX # 714-246-4272

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Stephen — Here are the MO's comments re: the August 3, 2000, Amendment to IND 48,929. This amendment proposed a new protocol as well as some new investigators. Please respond to these comments in an Amendment to the IND. Feel free to call me if you have any questions about these issues. Thanks.

Mike

Deficiency/Problem List:

1) *Names and qualifications of the Principal Investigators and Forms 1572 should be submitted for review when available and prior to initiation of the study.*

2) *Cardiac and pulmonary exclusions are included because of the use of a beta-blocker in the study design. This means the study medication may not be adequately evaluated for safety and efficacy in these populations in this particular protocol.*

3) *Significant bias will be introduced into this protocol because of its investigator-only masked design. This will limit the validity of collected data to establish the safety and IOP lowering efficacy of AGN 192024 0.03%.*

4) *Disagree with Sponsor's plan to establish equivalence. To establish equivalence between the groups, a 95% confidence interval should be obtained with the majority of data points showing less than 1 mm Hg difference and all data points showing less than 1.5 mm Hg difference.*

   The protocol as submitted allows for comparison of only one complete set of time points (T_0, T_0 + 2 hrs, T_0 + 8 hours, T_0 + 12 hours, T_0 + 16 hours, T_0 + 20 hours, and T_0 + 24 hours). To establish equivalence between products, the Agency expects at minimum, comparative evaluations at Baseline, Week 2, Week 4, Week 8, and Week 12.

5) *The agency does not currently accept latanoprost as an active control for the establishment of efficacy.*

HTL FDA Corresp.
SB

ALLERGAN

REGULATORY AFFAIRS

INTEROFFICE MEMORANDUM

TO: A. Batoosingh, J. Cheetham, K. Chen, C. Felix, A. VanDenburgh

FROM: S. Buxbaum/L. Gryziewicz,

SUBJECT: Telecon with FDA October 6, 1999: HTL and Brimonidine Purite Statistical Analysis Plans, HTL/Timolol Clinical Development, Brimonidine Pediatric

DATE: October 12, 1999

COPIES: A. Aswad, G. Beck, M.-J. Branin, J. Gibson, J. Injejikian, L. Kaplan, P. Kresel, N. Li, T. Lin, E. Lippa, S. Martin, O. Olejnik, A. Rosenthal, J. Wang
M. Beekman, I. Bossowska, G. Cook, M. Manini, J. Nelson, M. Rogan, U. Junghanns

---

A telecon with FDA took place on October 6, 1999. Representing Allergan were Amy Batoosingh, Steve Buxbaum, Janet Cheetham, Kuankuan Chen, Carlos Felix, Lewis Gryziewicz and Amanda VanDenburgh. Representing FDA were:

Wiley Chambers	Deputy Director
William Boyd	Medical Reviewer
Joanne Holmes	Medical Reviewer
Stan Lin	Biostatitician
Lori Gorski	Project Management
Raphael Rodriguez	Project Management

1. HTL and Brimonidine Purite Statistical Analysis Plans

a. *Statistical treatment*

- For each group, at each time point, at each week, FDA wants to see the 95% confidence interval around actual observed IOP results (means). Construct the confidence intervals for each of the pairwise comparisons without adjustment. FDA does not care about change from baseline.

- The definition of "equivalence" for regimens or products is: The majority of the confidence intervals are within 1 mm Hg, and all confidence intervals are within 1.5 mm Hg. If any other definitions are used, they need to be discussed with FDA.

Allergan action:
(1) Include analysis of mean IOPs at each timepoint in the main tables
(2) Include analysis of mean changes from baseline at each timepoint in the appendix

- To evaluate efficacy, FDA will accept intent to treat/last observation carried forward (ITT/LOCF) and per protocol (PP) on observed cases analyses, performed on all parameters. ITT/LOCF will be performed on Hour 0 and diurnal IOP as well. Whichever we want to designate as our primary efficacy analysis (PP or ITT/LOCF) is acceptable. ITT refers to all randomized subjects whether or not they actually received drug.

Allergan action:
(1) Include PP analysis of IOP in the main tables
(2) Include ITT/LOCF analysis of Hour 0 and each timepoint of the diurnals in the appendix

- Look for investigator interactions only for IOP at p=0.1.

- Using either of the statistical treatments, list the mean IOP reduction results by investigator, not by site. Descriptive statistics only, without p-values, is acceptable.

Allergan action:
(1) Include investigator interactions, based on pooling investigators per site built in the statistical model, in the appendix
(2) Include the summary of IOP reduction by investigator using a PP analysis in the appendix

b. *Safety parameters*

- Visual acuity: The stratification was listed correctly in the table but not in the text, i.e., changes (worsening and improvement) of ± >2 lines, 2 lines, 1 line etc.

- Cup/disc ratio: This should be described like VA, i.e., ± >0.2, 0.2 etc.

Allergan action:
(1) Generate and include this tabulation in the main tables

- AEs: FDA will look at all AEs combined, no matter the causality assessment. We can sort them by body system.

Allergan action:
(1) Include all AEs tabulated by descending order of frequency and body system in the main tables
(2) In addition to the tabulations already planned, put treatment-related AEs and tabulation by severity in the appendix

- Visual fields: Our proposal is satisfactory. In the future, Dr. Chambers suggested we look at 5 point changes with p=0.05 (as was discussed with memantine).

Allergan action: (1) Currently, these studies may not have a sufficient number of VFs per patient to do this analysis. This analysis will not be included in the NDA but may be performed in the future for exploratory purposes.

c. *Subgroup analyses*

- Age: 2 groups, i.e., <65, ≥65
- Gender
- Iris color: light or dark
- These breakdowns need to be done on IOP and AEs, using one of the analysis populations (ITT or PP). We do not need to break out race.

Allergan action: (1) Include these subgroup analyses based on PP in the appendix. We will do this analysis on pooled data from the pivotal studies.

d. *Electronic format for clinical data*

- Whatever format we create the data in is acceptable to submit, e.g., SAS version 6.12. FDA wants SAS transport files with copies of the program used.
- Sections 11 and 12 (CRFs and data listings) of the NDA can be submitted in electronic format if we wish.
- FDA wants to see actual CRFs for all discontinued subjects regardless of the reason for discontinuation.
- If we believe FDA will ask for CRFs for patients with serious AEs we may want to include them in the NDA instead of waiting for FDA to ask.

Allergan action: (1) We will submit CRFs for all discontinued patients and those with SAEs in electronic format only. We will use the format for data listings that has been used in previous FDA submissions.

We informed FDA about the problem with the Athens, Greece site for the 192024-502 study, which was adversely affected by the recent earthquake. We indicated that we were adding additional subjects to replace those lost to follow up. FDA asked if we really needed to replace them because of statistical considerations (were we so close with the number of subjects), and we indicated we had additional subjects already screened and this would only delay us about five weeks.

2. HTL/timolol combination

- With respect to our pre-IND/end of phase 2 briefing package, we should include all the information from the HTL monotherapy studies on which we based our assumptions. We indicated that we would have statistical tables from the 3-month analyses.

- FDA accepted our assertion that we would determine whether the combination product would be dosed once or twice daily based on the results of the monotherapy studies. Dr. Chambers made a passing comment about timolol being a twice-daily drug. He also asked, if we intend to test the combination once daily, when we planned on dosing (morning or evening). He then went on to indicate that, since β-blockers are not given at night, we would have to dose in the morning.

- We indicated that we were not planning on conducting further dose-response studies. Dr. Chambers hesitantly indicated that this was acceptable.

- We indicated that we are planning on doing one clinical PK study first, followed by two identical phase 3 studies, all with three-arm study designs. Dr. Chambers indicated that a total of 300 patients on the combination in the phase 3 studies is "bare minimum." When pressed about the need to explore systemic PK parameters in the PK study, Dr. Chambers indicated that their biopharmaceutics group is looking at historical existing data on systemic absorption after topical dosing. If they find the extent of absorption sufficiently low, systemic safety parameters might not need to be monitored. However, this analysis has not yet been done, so this testing is still required. When asked about the need for TDM, FDA suggested that this would be dependent on what we find in the HTL monotherapy studies.

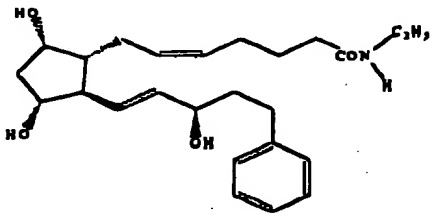
3. ALPHAGAN Pediatric Protocol

- Intraocular pressure will be the primary parameter for the pediatric trial.

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03%

DESCRIPTION

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is a synthetic prostamide analog with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is $C_{25}H_{37}NO_4$. Its chemical structure is:



Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. **LUMIGAN™** is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

Each mL contains: Active: bimatoprost 0.3 mg; Preservative: Benzalkonium chloride 0.05 mg; Inactives: Sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bimatoprost is a prostamide, a synthetic structural analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

Pharmacokinetics

Absorption:

After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and were below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing. Mean C_{max} and $AUC_{0\text{-}24hr}$ values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. There was no significant systemic drug accumulation over time.

Distribution
Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism
Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation,
N-deethylation and glucuronidation to form a diverse variety of metabolites.

Elimination
Following an intravenous dose of radiolabeled bimatoprost (3.12 µg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

Clinical Studies:
In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% once daily (in the evening) was 7-8 mmHg.

INDICATIONS AND USAGE

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product.

WARNINGS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% has been reported to cause changes to pigmented tissues. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.

LUMIGAN™ may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has also been reported in association with the use of **LUMIGAN™**.

LUMIGAN™ may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

PRECAUTIONS

General:
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for several months to years (see Warnings). Typically the brown pigmentation around the pupil is expected to spread concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. The increase in brown iris pigment is not expected to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor freckles of the iris are expected to be affected by treatment.

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN™** should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

LUMIGAN™ has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

LUMIGAN™ should not be administered while wearing contact lenses.

LUMIGAN™ has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

Information for Patients:
Patients should be informed that **LUMIGAN™** has been reported to cause increased growth and darkening of eyelashes and darkening of the skin around the eye in some patients. These changes may be permanent.

Some patients may slowly develop darkening of the iris, which may be permanent.

When only one eye is treated, patients should be informed of the potential for a cosmetic difference between the eyes in eyelash length, darkness or thickness, and/or color changes of the eyelid skin or iris.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

Contact lenses should be removed prior to instillation of **LUMIGAN™** and may be reinserted 15 minutes following its administration. Patients should be advised that **LUMIGAN™** contains benzalkonium chloride, which may be absorbed by soft contact lenses.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Carcinogenesis, Mutagenesis, Impairment of fertility:
Carcinogenicity studies were not performed with bimatoprost.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 103 times the recommended human exposure based on blood AUC levels).

Pregnancy: Teratogenic effects: ***Pregnancy Category C.***
In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost, which achieved at least 33, or 97 times, respectively, the intended human exposure based on blood AUC levels.

At doses 41 times the intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of LUMIGAN™ administration in pregnant women. Because animal reproductive studies are not always predictive of human response, LUMIGAN™ should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers:
It is not known whether LUMIGAN™ is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when LUMIGAN™ is administered to a nursing woman.

Pediatric use:
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

In clinical trials, the most frequent events associated with the use of LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% occurring in approximately 15% to 45% of patients, in descending order of incidence, included conjunctival hyperemia, growth of eyelashes, and ocular pruritus. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3 to 10% of patients, in descending order of incidence, included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, ocular irritation, and eyelash darkening. The following ocular adverse events reported in approximately 1 to 3% of patients, in descending order of incidence, included: eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 10% of patients were infections (primarily colds and upper respiratory tract infections). The following systemic adverse events reported in approximately 1 to 5% of patients, in descending order of incidence, included headaches, abnormal liver function tests, asthenia and hirsutism.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m^2 is at least 70 times higher than the accidental dose of one bottle of LUMIGAN™ for a 10 kg child.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 4 hours after the first administration with maximum effect reached within approximately 8 to 12 hours.

LUMIGAN™ may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is supplied sterile in opaque white low density polyethylene ophthalmic dispenser bottles with turquoise polystyrene caps in the following sizes: 2.5 mL fill in 8 mL container – NDC 0023-9187-03, 5mL fill in 8 mL container - NDC 0023-9187-05, or 7.5 mL fill in 8 mL container - NDC 0023-9187-07.

Rx only

Storage: LUMIGAN™ should be stored in the original container at 15° to 25°C (59° to 77°F).

Revised March 2001

ATTACHMENT D

U.S. Patent and Trademark Office
OFFICE OF FINANCE

Return To:
USPTO Home Page
Finance Home Page

Maintenance Fee Statement

5688819

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,688,819	183	850	----	08/605,567	11/18/97	02/22/96	04	NO	PAID

ITEM NBR	ATTY DKT NUMBER
1	16955DIV2CIP

Return to USPTO Home Page Return to Office of Finance Home Page

US005688819A

United States Patent [19]

Woodward et al.

[11] Patent Number: 5,688,819

[45] Date of Patent: *Nov. 18, 1997

[54] **CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS**

[75] Inventors: **David F. Woodward**, El Toro; **Steven W. Andrews**, Rancho Santa Marguerita; **Robert M. Burk**, Irvine; **Michael E. Garst**, Newport Beach, all of Calif.

[73] Assignee: **Allergan**, Waco, Tex.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,607,978.

[21] Appl. No.: **605,567**

[22] Filed: **Feb. 22, 1996**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 371,339, Jan. 11, 1995, Pat. No. 5,607,978, which is a continuation of Ser. No. 154,244, Nov. 18, 1993, abandoned, which is a division of Ser. No. 948,056, Sep. 21, 1992, Pat. No. 5,352,708.

[51] **Int. Cl.**[6] **A61K 31/135**; A61K 31/44; A61K 31/38; A61K 31/34

[52] **U.S. Cl.** **514/357**; 514/438; 514/471; 514/514; 514/530; 514/548; 514/549; 514/551; 514/573; 514/613; 514/617; 514/659; 514/646; 514/729

[58] **Field of Search** 514/357, 530, 514/573, 613, 659, 729, 646, 438, 471, 514, 548, 549, 551, 617; 546/337; 560/121; 562/503, 504, 510; 564/189, 453, 454; 568/838

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,055,602	10/1977	Nelson .	
4,171,331	10/1979	Biddlecom et al. .	
4,183,870	1/1980	Caton et al. .	
4,599,353	7/1986	Bito .	
4,994,274	2/1991	Chan et al. .	
5,034,413	7/1991	Chan et al. .	
5,352,708	10/1994	Woodward et al.	514/729
5,510,383	4/1996	Bishop et al.	514/530
5,545,665	8/1996	Burk	514/530
5,587,391	12/1996	Burk	514/357
5,607,978	3/1997	Woodward et al.	514/646

FOREIGN PATENT DOCUMENTS

0 093 380	11/1983	European Pat. Off. .
0 102 230	7/1984	European Pat. Off. .
0 253 094	1/1988	European Pat. Off. .
0 364 417	1/1989	European Pat. Off. .
0 453 127	10/1991	European Pat. Off. .
2 312 240	12/1976	France .
2 386 523	11/1978	France .
2 402 644	3/1979	France .
27 21 534	12/1977	Germany .
68 940	2/1974	Luxembourg .
90/02553	3/1990	WIPO .
92/08465	5/1992	WIPO .

OTHER PUBLICATIONS

Prostaglandins: vol. 13, No. 5, May 1977, Stoneham, MA, pp. 837–843, H.C. Arndt, "The Synthesis and Biological Activity of Prostaglandins Analogs Containing Spiroocyclic Rings".

Tetrahedron: Vo. 32, 1976, Oxford GB, pp. 2747–2752, P. De Clercqet al, "Cyclopentanones–VXL, Prostaglandin Synthesis Involving Catalytic Hydrogenation of 2,3–Dialkyl–4–Hydroxy–2–Cyclopentenones".

Bito, L.Z., "Prostaglandins and Related Compounds as Potential Ocular Therapeutic Agents", Biological Protection with Prostaglandins (Cohen, M.M., ed., Boc Raton, FL, CRC Press Inc., 1985, pp. 231–252.

Bito, L.Z., "Prostaglandins, Old Concepts and New Perspectives," Arch Oph., vol. 105, Aug. 1987 pp. 1036–1039.

Starr, M.S., "Further Studies on the Effect of Prostaglandin on Intraocular Pressure in the Rabbit", Exp. Eye Res., (1971) 170–177.

Nilsson, Siv F.E., et al, "PGF2a Increases Uveoscleral Outflow", ARVO Abstract, p. 284, Invest. Ophthalmol. Vis. Sci. 28 (suppl) (1987).

Bito, L.Z., "Prostaglandins, Other Eicosanoids, and Their Derivatives as Potential Antiglaucoma Agents", Applied Pharmacology in the Medical Treatment of Glaucoma, pp. 477–505, 1984.

Primary Examiner—Jose G. Dees
Assistant Examiner—Mary C. Cebulak
Attorney, Agent, or Firm—Robert J. Baran; Martin A. Voet; Howard R. Lambert

[57] **ABSTRACT**

The present invention provides cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds, which may be substituted in the 1-position with amino, amido, ether or ester groups, e.g., a 1-OH cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compound. The cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compounds of the present invention are potent ocular hypotensives, and are particularly suitable for the management of glaucoma. Moreover, the cyclopentane heptanoic, 2-(cycloalkyl or arylalkyl) compounds of this invention are smooth muscle relaxants with broad application in systemic hypertensive and pulmonary diseases; smooth muscle relaxants with application in gastrointestinal disease, reproduction, fertility, incontinence, shock, etc.

20 Claims, No Drawings

CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS

CROSSREFERENCE TO RELATED APPLICATIONS

This patent application is a continuation-in-part of U.S. patent application Ser. No. 08/371,339, filed on Jan. 11, 1995 now U.S. Pat. No. 5,607,978 which is a continuation of U.S. patent application Ser. No. 08/154,244 which was filed on Nov. 18, 1993, now abandoned, which is a divisional of U.S. patent application Ser. No. 07/948,056, filed on Sep. 21, 1992, now U.S. Pat. No. 5,352,708 issued on Oct. 4, 1994, all of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention provides cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds, which may be substituted in the 1-position with amino, amido, ether or ester groups, e.g., a 1-OH cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compound. The cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compounds of the present invention are potent ocular hypotensives, and are particularly suitable for the management of glaucoma. Moreover, the cyclopentane heptanoic, 2-(cycloalkyl or arylalkyl) compounds of this invention are smooth muscle relaxants with broad application in systemic hypertensive and pulmonary diseases; smooth muscle relaxants with application in gastrointestinal disease, reproduction, fertility, incontinence, shock, etc.

2. Description of the Related Art

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical b-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Prostaglandins were earlier regarded as potent ocular hypertensives; however, evidence accumulated in the last two decades shows that some prostaglandins are highly effective ocular hypotensive agents and are ideally suited for the long-term medical management of glaucoma. (See, for example, Starr, M. S. *Exp. Eye Res.* 1971, 11, pp. 170–177; Bito, L. Z. *Biological Protection with Prostaglandins* Cohen, M. M., ed., Boca Raton, Fla, CRC Press Inc., 1985, pp. 231–252; and Bito, L. Z., *Applied Pharmacology in the Medical Treatment of Glaucomas* Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477–505). Such prostaglandins include $PGF_{2\alpha}$, $PGF_{1\alpha}$, PGE_2, and certain lipid-soluble esters, such as C_1 to C_5 alkyl esters, e.g. 1-isopropyl ester, of such compounds.

In the U.S. Pat. No. 4,599,353 certain prostaglandins, in particular PGE_2 and $PGF_{2\alpha}$ and the C_1 to C_5 alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in glaucoma management.

Although the precise mechanism is not yet known, recent experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et al., *Invest. Ophthalmol. Vis. Sci.* 28 (suppl), 284 (1987)].

The isopropyl ester of $PGF_{2\alpha}$ has been shown to have significantly greater hypotensive potency than the parent compound, which was attributed to its more effective penetration through the cornea. In 1987 this compound was described as "the most potent ocular hypotensive agent ever reported." [See, for example, Bito, L. Z., *Arch. Ophthalmol.* 105, 1036 (1987), and Siebold et al., *Prodrug* 5, 3 (1989)].

Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular $PGF_{2\alpha}$ and its prodrugs, e.g. its 1-isopropyl ester, in humans. The clinical potential of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma, is greatly limited by these side effects.

Certain phenyl and phenoxy mono, tri and tetra nor prostaglandins and their 1-esters are disclosed in European Patent Application 0,364,417 as useful in the treatment of glaucoma or ocular hypertension.

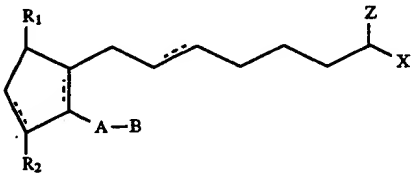
In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending U.S. Ser. No. 386,835 (filed 27 Jul. 1989), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl $PGF_{2\alpha}$. Intraocular pressure reducing 15-acyl prostaglandins are disclosed in the copending application U.S. Ser. No. 357,394 (filed 25 May 1989). Similarly, 11,15-9,15- and 9,11-diesters of prostaglandins, for example 11,15-dipivaloyl $PGF_{2\alpha}$ are known to have ocular hypotensive activity. See the co-pending patent applications U.S. Ser. No. 385,645 filed 27 Jul. 1990, now U.S. Pat. No.

4,494,274; 584,370 which is a continuation of U.S. Ser. No. 386,312, and 585,284, now U.S. Pat. No. 5,034,413 which is a continuation of U.S. Ser. No. 386,834, where the parent applications were filed on 27 Jul. 1989. The disclosures of these patent applications are hereby expressly incorporated by reference.

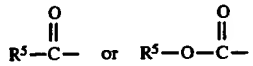
SUMMARY OF THE INVENTION

We have found that certain cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds and derivatives thereof wherein the carboxylic acid group is replaced by a non-acidic substituent have pronounced effects on smooth muscle and are potent ocular hypotensive agents. We have further found that such compounds, in certain instances, may be significantly more potent than their respective parent compounds and, in the case of glaucoma surprisingly, cause no or significantly lower ocular surface hyperemia than the parent compounds.

The present invention relates to methods of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive, allergic disease, shock and ocular hypertension which comprises administering an effective amount of a cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compound represented by the formula I

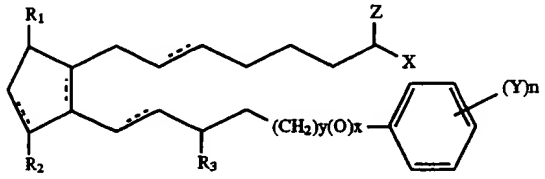


wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or akylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of —OR^4 and —$N(R^4)_2$ wherein R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,



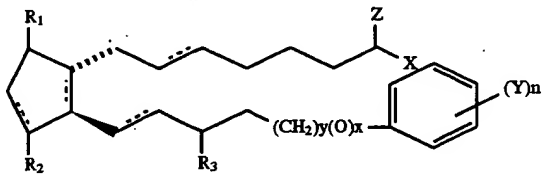
wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; one of R_1 and R_2 is =O, —OH or a —$O(CO)R_6$ group, and the other one is —OH or —$O(CO)R_6$, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or —$(CH_2)mR_7$ wherein m is 0 or an integer of from 1 to 10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided, however, that when B is not substituted with a pendant heteroatom-containing radical, and Z is =O, then X is not —OR^4. (That is, the cycloalkyl or hydrocarbyl aryl or heteroaryl radical is not substituted with a pendant radical having an atom other than carbon or hydrogen.)

More preferably the method of the present invention comprises administering a cyclopentane heptanoic acid, 2-(phenyl alkyl or phenyloxyalkyl) represented by the formula II



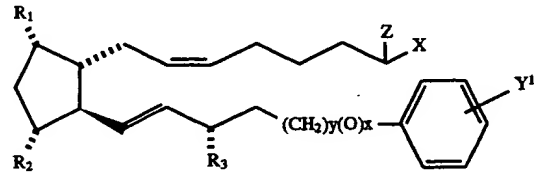
wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, e.g. fluoro, chloro, etc., nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, etc. and n is 0 or an integer of from 1 to about 3 and R_3 is =O, —OH or —$O(CO)R_6$ wherein R_6 is as defined above. Preferably, n is 1 or 2.

Preferably the compound used in the above method of treatment is a compound of formula (III).



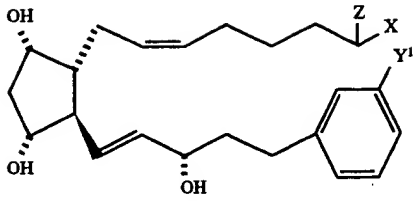
wherein hatched lines indicate a configuration, solid triangles are used to indicate β configuration

In another aspect, the present invention relates to a method of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases, shock and ocular hypertension which comprises administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (IV)



wherein Y^1 is Cl or trifluoromethyl and the other symbols and substituents are as defined above, in combination with a pharmaceutical carrier.

Finally, the method of the present invention relates to a method of treating cardiovascular, pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases, shock and ocular hypertension which comprises administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula V



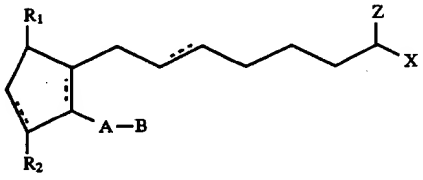
and the 9-and/or 11- and/or 15 esters thereof.

In a further aspect, the present invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formulae (I), (II), (III), (IV) or (V) wherein the symbols have the above meanings, or a pharmaceutically acceptable salt thereof in admixture with a non-toxic, pharmaceutically acceptable liquid vehicle.

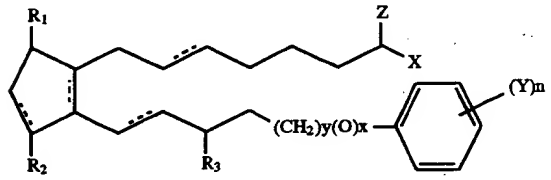
In a still further aspect, the present invention relates to cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds of the above formulae, wherein the substituents and symbols are as defined hereinabove, or a pharmaceutically acceptable salt of such compounds.

DETAILED DESCRIPTION OF THE INVENTION

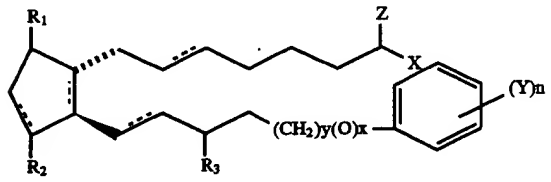
The present invention relates to the use of cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds as therapeutic agents, e.g. as ocular hypotensives. These therapeutic agents are represented by compounds having the formula I,



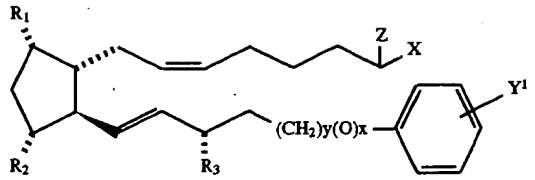
as defined above. The preferred nonacidic cyclopentane heptanoic acid, 2-(phenyl alkyl or phenyloxyalkyl) compounds used in accordance with the present invention are encompassed by the following structural formula (II)



wherein the substituents and symbols are as hereinabove defined. More preferably the compounds are represented by formula (III).

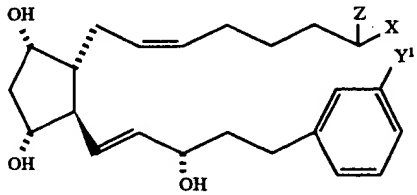


wherein the substituents and symbols are as defined above. More preferably, the compounds utilized in the present invention are compounds represented by the formula (IV)



wherein the substituents and the symbols are as defined above.

Most preferably the present invention utilizes the novel compounds of the formula (V)



and their 9- and/or 11- and/or 15-esters.

In all of the above formulae, as well as in those provided hereinafter, the dotted lines on bonds between carbons 5 and 6 (C-5), between carbons 13 and 14 (C-13), between carbons 8 and 12 (C-8), and between carbons 10 and 11 (C-10) indicate a single or a double bond which can be in the cis or trans configuration. If two solid lines are used that indicates a specific configuration for that double bond. Hatched lines at positions C-9, C-11 and C-15 indicate the α configuration. If one were to draw the β configuration, a solid triangular line would be used.

In the compounds used in accordance with the present invention, compounds having the C-9 or C-11 or C-15 substituents in the α or β configuration are contemplated. As hereinabove mentioned, in all formulas provided herein broken line attachments to the cydopentane ring indicate substituents in the a configuration. Thickened solid line attachments to the cyclopentane ring indicate substituents in the β configuration. Also, the broken line attachment of the hydroxyl group or other substituent to the C-11 and C-15 carbon atoms signifies the α configuration.

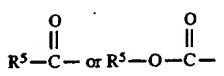
For the purpose of this invention, unless further limited, the term "alkyl" refers to alkyl groups having from one to ten carbon atoms, the term "cycloalkyl" refers to cycloalkyl groups having from three to seven carbon atoms, the term "aryl" refers to aryl groups having from four to ten carbon atoms. The term "saturated or unsaturated acydic hydrocarbon group" is used to refer to straight or branched chain, saturated or unsaturated hydrocarbon groups having from one to about 6, preferably one to about 4 carbon atoms. Such groups include alkyl, alkenyl and alkynyl groups of appropriate lengths, and preferably are alkyl, e.g. methyl, ethyl, propyl, butyl, pentyl, or hexyl, or an isomeric form thereof.

The definition of R_6 may include a cyclic component, $-(CH_2)_mR_7$, wherein n is 0 or an integer of from 1 to 10, R_7 is an aliphatic ring from about 3 to about 7 carbon atoms, or an aromatic or heteroaromatic ring. The "aliphatic ring" may be saturated or unsaturated, and preferably is a saturated ring having 3–7 carbon atoms, inclusive. As an aromatic ring, R_7 preferably is phenyl, and the heteroaromatic rings have oxygen, nitrogen or sulfur as a heteroatom, i.e. R_7 may be thienyl, furanyl, pyridyl, etc. Preferably m is 0 or an integer of from 1 to 4.

Z is =O or represents two hydrogen atoms.

X may be selected from the group consisting of $-OR^4$ and $-N(R^4)_2$ wherein R^4 is selected from the group con-

sisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,



wherein R^5 is a lower alkyl radical having from one to six carbon atoms.

Preferred representatives of the compounds within the scope of the present invention are the compounds of formula V wherein X is —OH, i.e. cyclopentane heptenoic acid, 5-cis-2-(3-αhydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$ and cyclopentane methylheptenoate-5-cis-2(3-αhydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5 dihydroxy, $[1_{6O},2_\beta,3_\alpha, 5_\alpha]$ and the 9- and/or 11- and/or 15-esters of this compound. (The numbered designations in brackets refer to the positions on the cydopentane ring.)

The following novel compounds may be used in the pharmaceutical compositions and the methods of treatment of the present invention.

(1) cyclopentane heptenol-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$,

(2) cyclopentane heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_{6\alpha}]$

(3) cydopentane N,N-dimethylheptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta, 3_\alpha,5_\alpha]$

(4) cyclopentane heptenyl methoxide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta, 3_\alpha,5_\alpha]$

(5) cyclopentane heptenyl ethoxide-5-cis-2-(3α-hydroxy-4-meta-chlorophenoxy-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha, 2_\beta, 3_\alpha,5_\alpha]$

(6) cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-meta-chlorophenoxy-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha, 2_\beta,3_\alpha, 5_\alpha]$

(7) cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-trifluoromethylphenoxy-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha, 2_\beta, 3_\alpha,5_\alpha]$

(8) cyclopentane N-isopropyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta, 3_\alpha,5_\alpha]$

(9) cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5 dihydroxy, $[1_\alpha,2_\beta, 3_\alpha,5_\alpha]$

(10) cyclopentane N-methyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta, 3_\alpha,5_\alpha]$

(11) cyclopentane heptenol-5-cis-2-(3α-hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha, 5_\alpha]$

(12) cydopentane heptenamide-5-cis-2-(3α-hydroxy-4-meta-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, $[1_\alpha, 2_\beta,3_\alpha,5_\alpha]$

(13) cyclopentane heptenol-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$

A pharmaceutically acceptable salt is any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Such salts are those formed with pharmaceutically acceptable cations, e.g., alkali metals, alkali earth metals, etc.

Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose cyclodextrin and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonidty adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place of or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001–5
preservative	0–0.10
vehicle	0–40
tonicity adjustor	0–10
buffer	0.01–10
pH adjustor	q.s. pH 4.5–7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered

application, such as in containers equipped with a dropper, to facilitate application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses.

Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five units doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20–35 ml.

The invention is further illustrated by the following non-limiting Examples.

EXAMPLE 1

Cyclopentane heptenoic acid, 5-cis-2-(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$

This compound may be purchased from Cayman Chemical Company of Ann Arbor, Michigan or synthesized by methods known in the art.

EXAMPLE 2

Cyclopentane methylheptenoate-5-cis-2(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy; $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$

To a stirred solution of cyclopentane heptenoic acid, 5-cis-2-(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$(24 mg. 0.0565 mmol) in acetone (0.6 ml) at room temperature was added 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) (40, ul, 0.27 mmol) and methyl iodide (20 ul, 0.32 mmol). The reaction turned yellow with the DBU addition. The reaction was maintained at room temperature for 6.5 hours, then was diluted with ethyl acetate (30 ml) and filtered through a plug of celite with the aid of ethyl acetate. After concentration in vacuo, the residue was flushed with ethylacetate (EtOAc) through a 20 mm×160 mm column of silica to give the desired methyl ester.

EXAMPLE 3

Cyclopentane heptenamide-5-cis-2-(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, $[1_\alpha,2_\beta,3_\alpha,5_\alpha]$

A mixture of the methyl ester of the compound of Example 1 (9.2 mg, 0.0222 mmol) and NH_4Cl (10 mg, 0.187 mmol) in NH_3 was heated at 80° C. for 12 hours. After cooling to room temperature, the solvents were evaporated and the residue was subjected to column chromatography to provide the named amide as 7.2 mg of a clear, colorless liquid.

EXAMPLE 4

Cyclopentane heptenoic acid-5-cis-2-(3α-hydroxyl-4-m-trifluoromethylphenoxy-1-trans-butenyl)-3,5-dihydroxy $[1\alpha,2\beta,3\alpha,5\alpha]$

This compound may be purchased from Cayman Chemical Company of Ann Arbor, Michigan or synthesized by methods known in the art.

EXAMPLE 5

Cyclopentane heptenamide-5-cis-2-(3α-hydroxyl-4-m-trifluoromethylphenoxy-1-trans-butenyl)-3, 5-dihydroxy $[1\alpha,2\beta,3\alpha,5\alpha]$

A mixture of the methyl ester of the compound of Example 4 (fluprostenol) and NH_4Cl in NH_3 is heated at 80° C. for 12 hours. After cooling to room temperature the solvents are evaporated and the residue is subjected to column chromatography to provide the named amide.

EXAMPLE 6

Measurement of intraocular pressure studies in dogs involved pneumatonometry performed in conscious, Beagle dogs of both sexes (10–15 kg). The animals remained conscious throughout the study and were gently restrained by hand. Drugs were administered topically to one eye as a 25 μL volume drop, the other eye received 25 μL vehicle (0.1% polysorbate 80:10 mM TRIS) as a control. 0.1% proparacaine was used for corneal anesthesia during tonometry. Intraocular pressure was determined just before drug administration and at 2, 4 and 6 hours thereafter on each day of the 5 day study. Drug was administered twice a day, with a 6 hour interval between doses that spanned the intraocular pressure measurement time frame. The result reported in Table 1, below.

TABLE 1

Comparison of effects of certain compounds of the invention on dog intraocular pressure. Values indicate mean changes from baseline intraocular pressure (±SEM) at predetermined times post-dosing. n = 8, *p < 0.05, **p < 0.01.

		INTRAOCULAR PRESSURE (mmHg) CHANGE AT PREDETERMINED TIMES (HR)			
COMPOUND	DOSE %	2	4	6	24
Example 1	0.01	−0.1 ± 0.8	−5.2 ± 1.4**	−4.3 ± 0.8	−4.4 ± 0.8
Example 1	0.1	−3.1 ± 0.8**	−3.2 ± 0.7	−2.7 ± 0.8	—
Example 3	0.01	−2.2 ± 1.0*	5.5 ± 1.1**	−4.0 ± 1.4*	2.7 ± 1.1*
Example 3	0.1	−1.3 ± 0.4*	2.3 ± 0.7**	−2.6 ± 0.6**	—
Example 5	0.1	−2.7 ± 0.8*	−3.4 ± 0.9*	−2.8 ± 0.4**	−2.1 ± 1.6*
Example 4	0.01	−0.9 ± 0.7	−2.5 ± 0.7*	−3.2 ± 0.7**	−1.3 ± 0.7
Fluprostenol	0.1	−1.3 ± 0.1	−2.1 ± 1.1	−2.7 ± 1.3	−3.1 ± 0.9*

EXAMPLE 7

Measurement of ocular surface hyperemia was visually assessed and scored according to the following schematic:

Hyperemia Score	Assigned Value
<1	1
1 slight	2
>1 < 2	3
2 moderate	4

-continued

Hyperemia Score	Assigned Value
>2 > 3	5
3 severe	6

(baseline scores for dogs are typically < 1)

The hyperemia value for each dog at a single time point (x) is obtained as follows: (treated eye value at hr x-baseline value)-(control eye value at hr x-baseline value). A composite value is then obtained by dividing the sum of the post-treatment measurement at each time point by the number of animals in the group: i.e. m where m=n measurements of ocular surface hyperemia. Ocular surface hyperemia is evaluated at the same time points as intraocular pressure measurement. It should be noted that untreated dog eyes frequently have a pink/red tone. Thus, values of <1 and 1 are essentially within the normal range. The results are reported in Table 2, below.

TABLE 2

Comparison of effects of certain compounds of the invention on dog ocular suface hyperemia. Values are composite scores as indicated in the methods.

COMPOUND	DOSE %	OCULAR SURFACE HYPEREMIA: COMPOSITE SCORE
Example 1	0.01	—
Example 1	0.1	0.33
Example 3	0.01	—
Example 3	0.1	0.81
Example 5	0.1	0.81
Example 4	0.01	1.08
Fluprostenol	0.1	1.50

It is clear that the compounds of Examples 1, 3 and 5, unexpectedly, show better efficacy at lowering IOP than Example 4 while showing less hyperemia.

The compounds of the invention may also be useful in the treatment of various pathophysiological diseases including acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heat failure, and angina pectoris, in which case the compounds may be administered by any means that effect vasodilation and thereby relieve the symptoms of the disease. For example, administration may be by oral, transdermal, parenterial, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes.

The compounds of the invention may be used alone, or in combination with other of the known vasodilator drugs.

The compounds of the invention may be formulated into an ointment containing about 0.10 to 10% of the active ingredient in a suitable base of, for example, white petrolatum, mineral oil and petroatum and lanolin alcohol. Other suitable bases will be readily apparent to those skilled in the art.

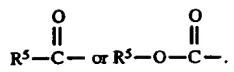
The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional dissolving or suspending the compounds, which are all either water soluble or suspendable. For administration in the treatment of the other mentioned pathophysiological disorders. The pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in liquid form that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as in buffered salt solution. In addition, stabilizers may be added.

In addition to being provided in a liquid form, for example in gelatin capsule or other suitable vehicle, the pharmaceutical preparations may contain suitable excipients to facilitate the processing of the active compounds into preparations that can be used pharmaceutically. Thus, pharmaceutical preparations for oral use can be obtained by adhering the solution of the active compounds to a solid support, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as sugars, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or caldum phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as inders such as starch, paste using for example, maize starch, wheat starch, rich starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, crosslinked polyvinyl pyrrolidone, agar, or algenic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which if desired, are resistant to gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Suitable formulations for intravenous or parenteral administration include aqueous solutions of the active compounds. In addition, suspensions of the active compounds as oily injection suspensions may be administered. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, soribitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

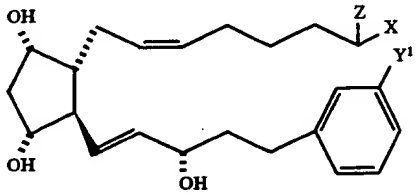
The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. For example, the present invention contemplates certain prodrugs of the above disclosed compounds, wherein R^4 is



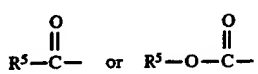
These compounds may be made by acylation or esterification of the corresponding hydroxy or amino derivative. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

We claim:

1. A method of treating ocular hypertension or glaucoma which comprises applying to the eye an amount sufficient to treat ocular hypertension or glaucoma of a compound represented by the formula V



wherein X is a radical selected from the group consisting —OR^4 and —$N(R^4)_2$ wherein R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,



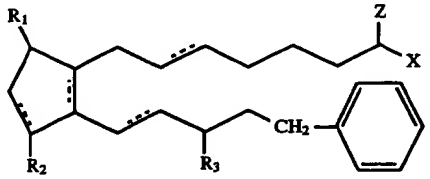
wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; Y' is Cl or trifluoromethyl and the 9- and/or 11- and/or 15 esters, thereof.

2. The method of claim 1 wherein Z is =O and X is selected from the group consisting of NH_2.

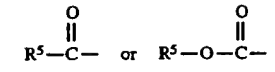
3. The method of claim 1 wherein Z is =O and X is selected from the group consisting of amido radicals.

4. The method of claim 1 wherein X is selected from the group consisting of NH_2 and OCH_3.

5. A method of treating ocular hypertension or glaucoma which comprises applying to the eye an amount sufficient to treat ocular hypertension or glaucoma of the formula

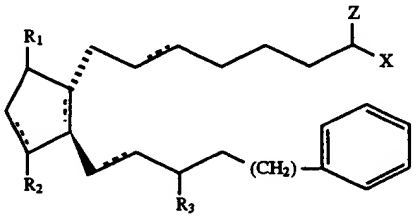


wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, X is a radical selected from the group consisting of —OR^4 and —$N(R^4)_2$ wherein R^4 is selected from the group consisting or hydrogen, a lower alkyl radical having from one to six carbon atoms,



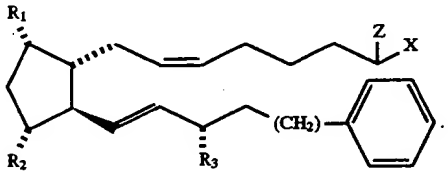
wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; R_3 is =O, —OH or —$O(CO)R_6$; one of R_1 and R_2 is =O, —OH or a —$O(CO)R_6$ group, and the other one is —OH or —$O(CO)R_6$, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or —$(CH_2)_mR_7$ wherein m is 0–10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; or a pharmaceutically-acceptable salt thereof, provided however that when Z is =O, then X is not —OR^4.

6. The method of claim 5 wherein said compound is represented by the formula

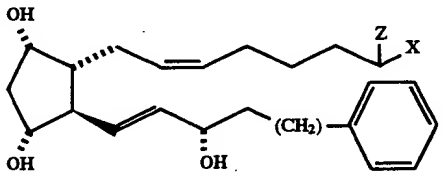


wherein hatched lines indicate the α configuration and solid triangles indicate the β configuration.

7. The method of claim 6 wherein said compound is represented by the formula



8. The method of claim 7 wherein said compound is represented by the formula



and the 9- and/or 11- and/or 15 esters, thereof.

9. The method of claim 8 wherein Z is =O and X is —$N(R^4)_2$.

10. The method of claim 9 wherein said compound is selected from the group consisting of

cyclopentane heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1_α,2_β,3_α,5_α];

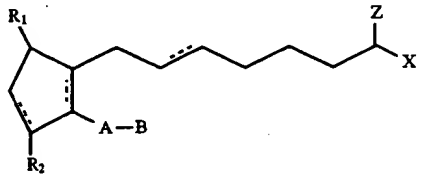
cyclopentane N,N-dimethylheptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N-isopropyl hepteneamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α]; and

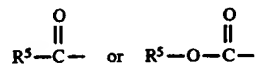
cyclopentane N-methyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α].

11. A method of treating cardiovascular pulmonary-respiratory, gastrointestinal, reproductive and allergic diseases and shock in a human which comprises administering to said human an effective amount of a compound of formula I



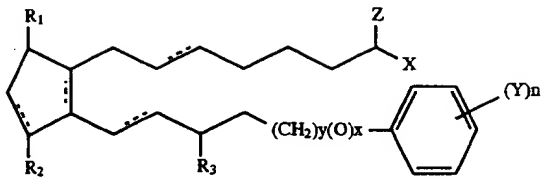
(I)

wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms, or an aryl radical selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of —OR^4 and —$N(R^4)_2$ wherein R^4 is selected from the group consisting or hydrogen, a lower alkyl radical having from one to six carbon atoms,



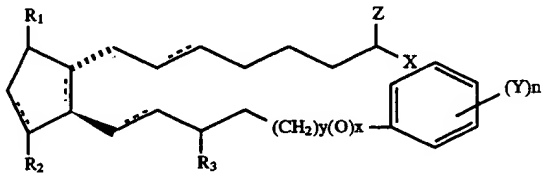
wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O or represents 2 hydrogen radicals; one of R_1 and R_2 is =O, —OH or a —$O(CO)R_6$ group, and the other one is —OH or —$O(CO)R_6$, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or —$(CH_2)_mR_7$ wherein m is 0–10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided however that when B is not substituted with a pendant heteroatom-containing radical and Z is =O, then X is not —OR^4.

12. The method of claim **11** wherein said compound represented by the formula (II)



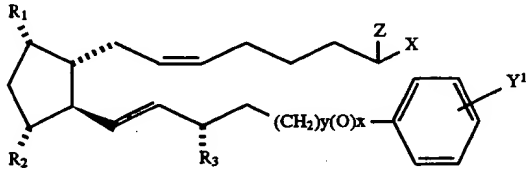
wherein y is 0 or 1, x is 0 or 1 and x+y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy,. alkyloxy, alkylcarboxy and halosubstituted alkyl, wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to 3 and R_3 is =O, —OH or —$O(CO)R_6$.

13. The method of claim **12** wherein said compound is represented by formula III.



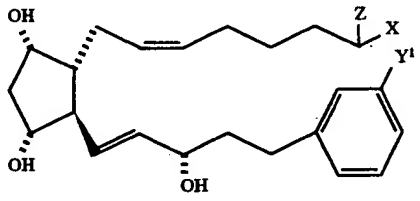
wherein hatched lines indicate the α configuration and solid triangles indicate the β configuration.

14. The method of claim **13** wherein said compound is represented by the formula IV.



wherein Y^1 is Cl or trifluoromethyl.

15. The method of claim **14** wherein said compound is a represented by the formula V



and the 9- and/or 11- and/or 15 esters, thereof.

16. The method of claim **15** wherein Z is =O and X is selected from the group consisting of NH_2 or OCH_3.

17. The method of claim **15** wherein Y^1 is Cl or trifluoromethyl, Z is =O and X is selected from the group consisting of alkoxy and amido radicals.

18. The method of claim **11** wherein said compound is selected from the group consisting of:

cyclopentane heptenol-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N,N-dimethylheptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenyl methoxide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenyl ethoxide-5-cis-2-(3α-hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-meta-trifluoromethyl-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N-isopropyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_b,3_α,5_α];

cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N-methyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane N-methyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenol-5-cis-2-(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenamide-5-cis-2-(3α-hydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α] and

cyclopentane heptenol-5-cis-2-(3α-hydroxy-5-phenylpentyl)3, 5-dihydroxy, [1_α,2_β,3_α,5_α].

19. The method of claim **17** wherein X is selected from the group consisting of NH_2 and OCH_3.

20. The method of claim **11** wherein said compound is selected from the group consisting of:

cyclopentane heptenoic acid-5-cis-2-(3α-hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-meta-chloro-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α];

cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-meta-trifluoromethyl-phenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α]; and

cyclopentane heptenonic acid-5-cis-2-(3α-hydroxy-4-meta-trifluoromethylphenoxy-1-trans-butenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α].

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,688,819

DATED : November 18, 1997

INVENTOR(S) : Woodward et al

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below: On the title page: Item [54] and Column 1, line 1,

Insert --NON-ACIDIC-- before "CYCLOPENTANE"

Column 6, line 38; delete "cydopentane" and insert in place thereof --cyclopentane--

Column 6, line 39; delete "a" and insert in place thereof --α--

Column 7, line 15; delete "1_{60}" and insert in place thereof --1α--

Column 7, line 18; delete "cydopentane" and insert in place thereof --cyclopentane--

Column 7, line 25; delete "$5_{6}\alpha$" and insert in place thereof --5α--

Column 7, line 26; delete "cydopentane" and insert in place thereof --cyclopentane--

Column 8, line 29; delete "tonidty" and insert in place thereof --tonicity--

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,688,819

DATED : November 18, 1997

INVENTOR(S) : Woodward et al

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 17, line 16; delete "1_a,2_b,3_a,5_a" and insert in place thereof --1_α, 2_β, 3_α,5_α--

Signed and Sealed this

Eighth Day of December, 1998

Attest:

Attesting Officer

BRUCE LEHMAN

Commissioner of Patents and Trademarks

ATTACHMENT E

STATEMENT IN ACCORDANCE WITH 37 CFR § 1.740(a)(10)

(a) U.S. Patent No. 5,688,819 issued on November 18, 1997.

(b) Application for investigation New Drug Exemption (IND) for Lumigan® (Bimatoprost) ophthalmic solution was effective on October 28, 1995 as IND. No. 48,929.

(c) New Drug Application (NDA) for Lumigan® (Bimatoprost) was initially submitted on September 18, 2000 as NDA 21-275.

(d) NDA 21-275 for Lumigan® (Bimatoprost) ophthalmic solution was approved on March 16, 2000.

ATTACHMENT F

Brief Description, in accordance with 37 CFR 1.740(a)(11), of significant activities undertaken by marketing applicant during regulatory review period with respect to LUMIGAN™.

On September 28, 1995, an Investigational Drug Application (IND), 48-929, was submitted to FDA. The application was received by FDA on September 29, 1995.

The first clinical trial conducted was a phase 2 study (192024-001), which began on October 31, 1995 and completed on December 22, 1995. The study was a five and one-half day safety and efficacy, dose-response pilot study evaluating bimatoprost 0.01%, 0.03% and 0.1% ophthalmic solution in subjects with open-angle glaucoma or ocular hypertension. The findings of this study were reported in the first Annual Report (November 11, 1996).

On September 20, 1996, a new clinical study protocol (192024-002) was submitted to FDA. This phase 2 study was a one-month safety and efficacy study of bimatoprost 0.003%, 0.01% and 0.03% ophthalmic solutions compared to its vehicle and timolol 0.5%, in subjects with open-angle glaucoma or ocular hypertension. This study was conducted over the period October 3, 1996 to February 2, 1997. Results of this study were reported in the second Annual Report (November 24, 1997).

In accordance with 21 CFR 312.33, the first Annual Report was submitted on November 11, 1996. Along with the Annual Report, an Information Amendment was submitted which contained three pre-clinical pharmacology study reports that presented data on cardiovascular and spontaneous motor activity of bimatoprost. Also included were three toxicology studies that detailed results of mutagenicity and acute intravenous pre-clinical studies.

On August 28, 1997, a new clinical study protocol (192024-004) was submitted to FDA. This phase 2 study was conducted to assess the safety and efficacy of bimatoprost 0.03% and AGN 192151 0.06% ophthalmic solutions compared to vehicle and latanoprost 0.005% in subjects with primary open-angle glaucoma or ocular hypertension. On September 2, 1997, the protocol was amended to add investigational review board information and a revised patient information and consent form. The study was initiated on September 8, 1997 and was completed January 1, 1998. A summary of the study results was presented in the third Annual Report (February 19, 1999).

On October 6, 1997, an Information Amendment was submitted which contained the stability study data for the preserved formulation of bimatoprost 0.03% ophthalmic solution. This formulation was evaluated in the phase 2 clinical study 192024-004.

On October 28, 1997, the phase 1 clinical study protocol 192024-006 was submitted to FDA. This study was conducted to investigate the pharmacokinetic profile of bimatoprost and the corresponding C1-acid (AGN 191522), and to evaluate the safety of bimatoprost 0.03% after one, seven, and fourteen days of ocular dosing in normal, healthy volunteers. The study began on October 16, 1997 and ended on October 30, 1997. The results of this study were also reported in the third Annual Report (February 19, 1999).

On November 11, 1997, the second Annual Report was submitted along with an Information Amendment containing several pharmacokinetics study reports. These pre-clinical studies evaluated the absorption, distribution, metabolism and elimination of bimatoprost and the corresponding C1-acid (AGN 191522).

On February 13, 1998, an End of Phase (EOP) 2 Meeting request, proposed for April 20, 1998, was submitted to the IND. The Briefing Package was sent to FDA on April 9, 1998. The meeting was held on April 30, 1998 and a summary of the meeting minutes was sent to FDA on June 4, 1998. The phase 3 pivotal study protocol was prepared based upon the EOP 2 commitments and sent to FDA for review on

September 22, 1998. The two pivotal study protocols (192024-008 and 192024-009) were submitted formally to the IND on December 8, 1998. On February 23, 1999, FDA sent a facsimile with comments on the 3-month mouse study discussed at the EOP 2 meeting. We submitted a complete response to these comments on March 23, 1999. Allergan also provided the Agency with other study reports committed to at the EOP 2 meeting.

In 1998, two phase 1 and one phase 2 clinical study protocols were filed to the IND. On March 30, 1998, the phase 2 protocol 192024-003 was submitted to evaluate the safety and efficacy of bimatoprost 0.03% ophthalmic solution compared with vehicle administered once-daily in the morning for 1 month in patients with open-angle glaucoma or ocular hypertension (study dates: 5/6/99 to 8/31/99). On June 10, 1998, the IND was amended with a phase 1 study (192024-007) to investigate the pharmacokinetic profile of bimatoprost and the corresponding C1-acid (AGN 191522), and to evaluate the safety of bimatoprost 0.03% after one, seven, and fourteen days of twice-daily ocular dosing in normal, healthy volunteers (study dates: 6/9/98 to 6/24/98). Study protocol 192024-005, which was a single-center, open-label study of the pharmacokinetics, mass balance and safety of ^{3}H-bimatoprost following a single intravenous administration in normal, healthy, male subjects was submitted on July 13, 1998 (study dates: 7/14/98 to 7/23/98). The results of the 192024-007 and 192024-005 studies were reported in the third Annual Report (February 19, 1999). On June 22, 1999, the final study reports for 192024-007 and 192024-005 were submitted to the IND. On May 14, 1999, a revision to the 192024-003 clinical study protocol was submitted to allow previous use of latanoprost. Results from the 192024-003 clinical study were reported in the fourth Annual Report (December 29, 1999).

On September 11, 1998, a carcinogenicity waiver request was sent to FDA. On November 5, 1999, a teleconference was held which included Lori Gorski and Dr. Andrea Weir of the FDA to discuss the waiver request. On November 16, 1998, additional data was submitted as requested by Dr. Weir. In a second teleconference

held on November 24, 1998, specific questions were presented to FDA regarding the design of the 6-month IV study in monkeys. (Meeting minutes of the November 24, 1998 teleconference were sent to FDA on January 8, 1999.) On December 8, 1998, Dr. Weir sent a facsimile in response to our questions. The carcinogenicity study protocols were then prepared and submitted to FDA on December 22, 1998, for review. In a telephone conversation on January 20, 1999, FDA requested additional information, which was provided the following day. A teleconference held on March 1, 1999, included a discussion of the timelines for completing these studies. On March 23, 1999, Allergan provided the Agency with certain study data committed to at the Carcinogenicity Waiver meeting on November 24, 1998. To further support our waiver request, a copy of the opinion from the European Agency for the Evaluation of Medicinal Products (EMEA) was submitted to the IND on March 29, 1999. As suggested by Dr. Weir in the December 8, 1998 facsimile, a justification was submitted (June 11, 1999) to terminate our 6-month intravenous toxicity study of bimatoprost in monkeys at 3 months based upon comparative systemic exposure data. The carcinogenicity waiver request was submitted for the New Drug Application (NDA) on August 14, 2000 as directed by Joanne Holmes, FDA Project Manager, in an e-mail dated January 11, 2000. This request included the completed 52-week toxicology study in rats and 21-month interim data summaries for the 2-year carcinogenicity studies in mice and rats. On September 1, 2000, an e-mail was received from FDA which granted the waiver request.

On September 17, 1998, a request was submitted for an EOP 2 Chemistry, Manufacturing and Controls (CMC) meeting proposed for November 12, 1998. On October 28, 1998, Raphael Rodriguez of FDA (Project Manager), called to request that the meeting be held on November 17, 1998 and stated that the Briefing Package must be sent in. That same day the Briefing Package was submitted. The EOP 2 meeting was held as scheduled and meeting minutes were sent to FDA on January 8, 1999. We obtained several agreements from FDA on the stability study design for use in the NDA.

On September 28, 1998, the final clinical study reports for the phase 1 studies 192024-001 and 192024-002 were submitted to the IND.

On February 19, 1999, the third Annual Report was submitted. Along with the Annual Report, an Information Amendment was sent which included the final clinical study report for the phase 2 study 192024-004. Several pharmacokinetics, pharmacology and toxicology study reports were also submitted.

On May 14, 1999, two phase 3 clinical study protocols (192024-501 and 192024-502) were filed to the IND. These studies were conducted outside of the United States and designed to meet foreign registration requirements. On June 22, 1999, comments from the Medical Officer on the study design were received. On August 11, 1999, a response to these comments was submitted to the IND. Additional comments were received on September 7, 1999, and responded to on October 15, 1999. The Project Manager confirmed the acceptability of the study designs in a November 10, 1999 e-mail. These studies began in February 1999.

Two clinical study protocols (192024-010 and 192024-012) were submitted to the IND on July 16, 1999. Study 192024-010 was a phase 3b trial to evaluate the safety and efficacy of bimatoprost 0.03% ophthalmic solution compared with latanoprost 0.005% (study dates: 6/28/99 to 5/31/00). The 192024-012 study was a phase 1 trial to assess the pharmacokinetics and safety of bimatoprost 0.03% ophthalmic solution in normal, healthy, elderly and young subjects (study dates: 7/9/99 to 9/26/99). On August 19, 1999, a response was submitted to an e-mail from Raphael Rodriguez of August 17,1999, to clarify that 192024-010 is a phase 3b study whose primary purpose was for publication. On September 21, 1999, an additional comment was received from the Medical Officer through Raphael Rodriguez which required no further action. Interim results of the phase 3b study and final results of the phase 1 study were reported in the fourth Annual Report (December 29, 1999).

On August 3, 1999, the final report for the 6-month toxicology study in rabbits was submitted to the IND.

A teleconference was held with the FDA on April 26, 1999, to discuss outstanding issues on a number of products. Prior to this teleconference, the synopses from three completed pharmacokinetics studies had been faxed to the FDA. The Agency was also informed that an elderly vs. young study was planned, and that at this time these four studies represented what was felt to be adequate for NDA filing. Dr. Chambers indicated that FDA's clinical pharmacologist (Dennis Bashaw) had not had a chance to look over the study synopses, and therefore they were unwilling at this time to offer an opinion. Allergan was to follow-up with the Agency at a later date. On August 13, 1999, an e-mail was received from Dennis Bashaw through Joanne Holmes with the Agency's questions concerning the clinical pharmacokinetics studies. The following week, a detailed clinical pharmacokinetics development plan for Lumigan was submitted to the Agency for comment. The response to FDA's comments was provided on November 19, 1999, which included copies of the completed pharmacokinetics studies. On September 9, 1999, a further request was made specifically asking the Agency to comment on the statistical analysis plan for the two pivotal studies (192024-008 and 192024-009). In a teleconference held on September 15, 1999, it was agreed that the statistical analysis plan for all the phase 3 studies (U.S. studies 192024-008 and 192024-009; international studies 192024-501 and 192024-502) will be discussed in a subsequent teleconference. That same day the statistical analysis plan for the international phase 3 studies was submitted to the IND. On October 6, 1999, the teleconference was held to again follow up outstanding issues on a number of products which included the statistical analysis plan for Lumigan. Final acceptance by the Agency of the plans for the U.S. and international phase 3 statistical analyses was received on November 10, 1999 and January 11, 2000, respectively.

On March 30, 1999, a request to preclear the tradename "Miragan" was submitted, but rejected on August 16, 1999. Another proposed tradename "Lumigan" was submitted for

consideration on August 19, 1999. The tradename "Lumigan" was accepted on February 5, 2001 as indicated in an e-mail from Michael Puglisi, Project Manager.

On December 29, 1999, the fourth Annual Report was submitted. Along with this submission, an Information Amendment was filed containing an extensive collection of toxicology, pharmacology and pharmacokinetics study reports. Also included were three new clinical study protocols (phase 1: 192024-011 and phase 3b: 192024-013 and 192024-014). In a separate document that same day and in accordance with 21 CFR 312.32, a safety report was also filed. On February 8, 2000, comments were received from the Medical Officer regarding the phase 3b trials. Our response was sent on May 24, 2000.

On February 1, 2000, a request was submitted for a Pre-NDA meeting to be held on March 27 or 28 to discuss the Clinical sections of the application. On March 9, 2000, a request was made to also discuss CMC issues. On March 14, 2000, the Clinical Briefing Package was sent to FDA. On March 22, 2000, the Agency requested CMC information to be sent as soon as possible and scheduled the Pre-NDA meeting for April 12, 2000. The CMC information was submitted on March 27, 2000. On April 4, 2000, the Agency requested additional CMC information which was provided on April 6, 2000. The Pre-NDA meeting was held on April 12, 2000, as scheduled, and the meeting minutes were submitted to FDA on May 24, 2000.

On February 17, 2000, an Information Amendment was submitted which included several pharmacology study reports. In May another Information Amendment was sent containing a pharmacology study report, the final clinical study report 192029-011 and a revision to the phase 3b trial 192024-014 to extend the study duration. A safety report was also filed in May. Two new clinical study protocols for phase 3b trials were filed in June and August (192024-015 and 192024-016, respectively). Comments were received from the Medical Officer on August 25, 2000, concerning the protocol for 192024-016.

On September 18, 2000, NDA 21-275 was received by FDA. Selected files were also submitted to FDA in electronic format over the next week (September 18 through September 26, 2000).

On September 22, 2000, Michael Puglisi of FDA (Project Manager), conveyed a request from Dr. Su Tso, FDA Chemistry Reviewer, to revise the 356h form to include the facility responsible for EtO sterilization. Additionally, revisions to the DMF authorization letters were requested to include details of the filing chronology and location of information. The updated 356h form was submitted to FDA on September 26, 2000. The revised DMF authorization letters were submitted once they became available.

On September 27, 2000, Dr. Tso requested a master index with greater detail than was originally submitted. The updated master index was regenerated and e-mailed to Dr. Tso before the end-of-day. On October 2, 2000, Dr. Tso requested details of the formulations used in the pre-clinical studies, confirmation of the container/closure configurations and labeling used on the stability samples, and requested confirmation of available test data. A response was submitted to FDA on October 10, 2000. This response also included copies of the various e-mails prepared in response to Dr. Tso's requests spanning September 22 through October 2, 2000.

On October 3, 2000, the application was accepted for filing and given a priority review classification by FDA.

On October 24, 2000, Dr. Tso called for the location of the BAK titration-to-failure report and to obtain clarification of the EtO residuals table. The report was located in the Microbiology section of the NDA, so a separate copy of the report was provided on October 26, 2000, along with clarification of the EtO residual table.

On October 27, 2000, Michael Puglisi conveyed a request from the Pharmacology Reviewer for a copy of the complete assay validation and individual subject data for the various pharmacokinetics studies. Additionally, the reviewer requested information on

the stability of the pharmacokinetics samples. The location of these reports within the original NDA and the stability information was provided on November 1, 2000.

On November 28, 2000, an information request was received from Dr. Tso. The request contained 31 questions or requests covering the drug substance, drug product and product labeling. On November 29, 2000, a teleconference with Dr. Tso was held to review each of these requests. A complete response to the majority (27 out of 31) of Dr. Tso's comments was submitted on December 8, 2000. On December 18, 2000, another teleconference was held with Dr. Tso to discuss this response. In the teleconference, Dr. Tso requested additional information to be provided for 4 out of the 27 responses submitted in our December 8, 2000 amendment. On December 29, 2000, a response was provided which addressed all the remaining requests (4 out of the original 31, and 4 out of the 27 responses).

On December 20, 2000, a request from the Pharmacology Reviewer was received through Michael Puglisi to provide details of the formulations used in the pre-clinical studies. Also the reviewer noted that a page was missing from one of the pre-clinical study reports. A response was submitted on December 21, 2000, which included details of the developmental formulations. The missing page of the study report was submitted once it became available (January 4, 2001).

On December 22, 2000, a facsimile was received from Michael Puglisi with a request from the Medical Officer for the location of specific data for study 192024-002. Steve Buxbaum, Director, Allergan Regulatory Affairs, called the Medical Officer to direct him to the location of this data. On December 27, 2000, the Medical Officer requested additional data for study 192024-003. This data was provided to FDA on December 28, 2000. Then on December 29, 2000, the Medical Officer requested the location of specific data for studies 192024-008 and 192024-009. Steve Buxbaum called the Medical Officer to direct him to the location of this data.

On January 3, 2001, a request was received from Zou Chen, Pharmacologist, concerning the safety of the residual solvents, related substances and container/closure extractables found in bimatoprost raw material and/or Lumigan. A detailed response was provided on January 11, 2001.

On January 9, 2001, Zou Chen requested justification of our statement in the labeling regarding exposure multiples. On January 16, 2001, we provided the Pharmacologist with a summary table of information which was included in the original NDA.

On January 16, 2001, a facsimile was received from Michael Puglisi with a request from the Microbiology Reviewer for specific information on the aseptic process for Lumigan. On January 25, 2001, a complete response was submitted to FDA. In a separate document that same day and in accordance with 21 CFR 314.50, the 120-day safety update was submitted to FDA. As part of this update, we submitted proposed labeling changes based upon the updated safety data.

On January 26, 2001, Michael Puglisi sent a facsimile with questions and comments from Dr. Hossein Khorshidi, Reviewing Chemist, and Dr. Tso regarding CMC issues related to bimatoprost and Lumigan. A teleconference was held on January 30, 2001, to obtain clarification and agreement prior to submitting a formal response, which was then sent on February 1, 2001. The revised quality control documents for the test methods were sent as they became available (February 12 and March 1, 2001).

On January 31, 2001, Zhou Chen requested clarification and some additional information regarding our response on January 16, 2001, regarding exposure multiples. Our clarifying response, which included the additional information, was submitted on February 1, 2001. The following day Zhou Chen called Steve Buxbaum and stated that he was unable to locate one of the study reports listed in our response. Later that day the referenced report was identified as incorrect and a copy of the proper report was sent in response.

On February 5, 2001, we received a request from Dr. Khorshidi for additional CMC information which was provided that same day.

On February 12, 2000, Dr. Khorshidi sent a facsimile detailing questions regarding the container/closure extractables and requesting more legible labeling for the immediate container. A teleconference was held on February 13, 2001, to discuss the Agency's comments regarding the extractables and to propose specifications. As agreed in the teleconference, the Agency would consider the justifications provided in the teleconference. On February 16, 2001, Steve Buxbaum followed up on the February 13, 2001 teleconference with our proposed specifications. This proposal was considered acceptable with the addition of a specific footnote. Subsequent to this teleconference and follow-up phone calls, we submitted our response with the agreed-upon specifications and revised labeling on February 20, 2001.

On February 13, 2001, we received a number of questions concerning commercial labeling components already in stock. The requested information was provided the following day.

On February 16, 2001, Dr. William Boyd of FDA (Medical Officer), sent a copy of the Agency's proposed package insert for Lumigan. After careful review of this labeling, we submitted a revision to this labeling on February 23, 2001, with a justification to support our position. After additional phone conversations, we submitted further justification on February 26, 2001, to support removal of the liver function test statement. On February 28, 2001, a teleconference was held to discuss our proposed package insert. The final draft version of the package insert was submitted to the Agency on March 1, 2001, with a follow-up submission on March 2, 2001, containing minor corrections. Subsequent to Office-level review of the package insert and a final telephone conversation with Dr. Chambers of FDA on March 14, 2001, the final version of the package insert was submitted to the Agency that afternoon.

On February 26, 2001, an impromptu teleconference was held to discuss changes we proposed to the container label regarding the fill volume statement. A formal submission of our requested labeling change was made that afternoon. On March 5, 2001, following a telephone conversation with Dr. Wiley Chambers and Michael Puglisi, we provided a commitment to remove the "slack fill" statement from the container label at the next printing to allow for larger type size.

On March 6, 2001, CMC information regarding the active pharmaceutical ingredient (API), bimatoprost, was sent to Marie Fadden, Consumer Safety Officer, in preparation for the Pre-Approval Inspection of Torcan (API manufacturer) to be conducted March 13 to 15, 2001. As part of this inspection, samples of the API were shipped to the Agency's Forensic Chemistry Center on March 20, 2001. The manufacturer information requested in Form FDA 2438g was sent under a separate cover on March 22, 2001.

On March 16, 2001, Allergan received its approval for Lumagan.

The above incidents and dates are set forth in Exhibit A, which is attached to and made a part of this Attachment F.

PATENT TERM EXTENSION

ATTACHMENT G

STATEMENT IN ACCORDANCE WITH 37 CFR § 1.740(a)(12)

Applicant is of the opinion that U.S. Patent 5,688,819 is eligible for extension under 35 U.S.C. § 156 because it satisfies all the requirements for such extension as follows:

I. (a) 35 U.S.C. § 156(a)

U.S. Patent No. 5,688,819 claims the use of compound Bimatoprost, i.e., cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1_α,2_β,3_α,5_α] in a method of treating ocular hypertension or glaucoma.

(b) 35 U.S.C. § 156(a)(1)

The term of U.S. Patent No. 5,688,819 has not expired before submission of this Application for Extension;

(c) 35 U.S.C. § 156(a)(2)

The term of U.S. Patent No. 5,688,819 has never been extended;

(d) 35 U.S.C. § 156(a)(3)

The Application of Extension is submitted by Allergan the owner of record of U.S. Patent No. 5,688,819

in accordance with the requirements of 35 U.S.C. § 156(d) and the guidelines of the United States Patent and Trademark Office;

(e) 35 U.S.C. § 156(a)(4)

Lumigan® having the active ingredient Bimatoprost, has been subject to a regulatory review period for its commercial marketing or use;

(f) 35 U.S.C. § 156(a)(5)(A)

The permission for commercial marketing or use of Lumigan®, after the regulatory review period is the first permitted commercial marketing or use of Bimatoprost, the active ingredient under the provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), under which such regulatory review period occurred; and

(g) 35 U.S.C. § 156(c)(4)

No other patent has been extended for the same regulatory period for the the active ingredient Bimatoprost.

II. The length of extension of the patent term of U.S. Patent 5,688,819 claimed by applicant is 907 days or 2.5 years, which will have the effect of extending the term of the patent after the date of approval of Bimatoprost to fourteen (14) years in accordance with 35 USC § 156(c)(3).

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) was from October 28, 1995 (the effective date of the IND) until March 16, 2001 which is 1,965 days or 5.4 years.

(b) The period of review, under 35 U.S.C. § 156(g)(1)(B)(i) was from October 28, 1995 (effective date of IND) until September 18, 2000 (NDA submission date), which
is 1,786 days or 4.9 years.

(c) The period of new drug application review under 35 U.S.C. § 156(g)(B)(ii) was from September 18, 2000 (NDA submission date) until March 16, 2000 (NDA approval date), which is 179 days or 0.5 years.

(d) Under 35 U.S.C. § 156 (c)(2), the period of extension may include only one half of the period determined under 35 U.S.C. § 156(g)(1)(B)(i), i.e., 893 days or 2.5 years (as per II(b) above).

(e) In compliance with 35 U.S.C. § 156(c)(3), the period remaining in the term of U.S. Patent No. 5,688,819 after NDA approval of Lumigan® i.e., from March 16, 2001 to September 21, 2012, i.e. 4206 days or 11.5 years, when added to the regulatory review period, i.e. 1068 days or 3.0 years, exceeds fourteen (14) years from the date of the approval of the approved product. Therefore, the applicant hereby claims an extension of the patent term of U.S. Patent 5,688,819 for 907 days or 2.5 years, to therefore expire on March 16, 2015.

On August 3, 1999, the final report for the 6-month toxicology study in rabbits was submitted to the IND.

A teleconference was held with the FDA on April 26, 1999, to discuss outstanding issues on a number of products. Prior to this teleconference, the synopses from three completed pharmacokinetics studies had been faxed to the FDA. The Agency was also informed that an elderly vs. young study was planned, and that at this time these four studies represented what was felt to be adequate for NDA filing. Dr. Chambers indicated that FDA's clinical pharmacologist (Dennis Bashaw) had not had a chance to look over the study synopses, and therefore they were unwilling at this time to offer an opinion. Allergan was to follow-up with the Agency at a later date. On August 13, 1999, an e-mail was received from Dennis Bashaw through Joanne Holmes with the Agency's questions concerning the clinical pharmacokinetics studies. The following week, a detailed clinical pharmacokinetics development plan for Lumigan was submitted to the Agency for comment. The response to FDA's comments was provided on November 19, 1999, which included copies of the completed pharmacokinetics studies. On September 9, 1999, a further request was made specifically asking the Agency to comment on the statistical analysis plan for the two pivotal studies (192024-008 and 192024-009). In a teleconference held on September 15, 1999, it was agreed that the statistical analysis plan for all the phase 3 studies (U.S. studies 192024-008 and 192024-009; international studies 192024-501 and 192024-502) will be discussed in a subsequent teleconference. That same day the statistical analysis plan for the international phase 3 studies was submitted to the IND. On October 6, 1999, the teleconference was held to again follow up outstanding issues on a number of products which included the statistical analysis plan for Lumigan. Final acceptance by the Agency of the plans for the U.S. and international phase 3 statistical analyses was received on November 10, 1999 and January 11, 2000, respectively.

On March 30, 1999, a request to preclear the tradename "Miragan" was submitted, but rejected on August 16, 1999. Another proposed tradename "Lumigan" was submitted for

consideration on August 19, 1999. The tradename "Lumigan" was accepted on February 5, 2001 as indicated in an e-mail from Michael Puglisi, Project Manager.

On December 29, 1999, the fourth Annual Report was submitted. Along with this submission, an Information Amendment was filed containing an extensive collection of toxicology, pharmacology and pharmacokinetics study reports. Also included were three new clinical study protocols (phase 1: 192024-011 and phase 3b: 192024-013 and 192024-014). In a separate document that same day and in accordance with 21 CFR 312.32, a safety report was also filed. On February 8, 2000, comments were received from the Medical Officer regarding the phase 3b trials. Our response was sent on May 24, 2000.

On February 1, 2000, a request was submitted for a Pre-NDA meeting to be held on March 27 or 28 to discuss the Clinical sections of the application. On March 9, 2000, a request was made to also discuss CMC issues. On March 14, 2000, the Clinical Briefing Package was sent to FDA. On March 22, 2000, the Agency requested CMC information to be sent as soon as possible and scheduled the Pre-NDA meeting for April 12, 2000. The CMC information was submitted on March 27, 2000. On April 4, 2000, the Agency requested additional CMC information which was provided on April 6, 2000. The Pre-NDA meeting was held on April 12, 2000, as scheduled, and the meeting minutes were submitted to FDA on May 24, 2000.

On February 17, 2000, an Information Amendment was submitted which included several pharmacology study reports. In May another Information Amendment was sent containing a pharmacology study report, the final clinical study report 192029-011 and a revision to the phase 3b trial 192024-014 to extend the study duration. A safety report was also filed in May. Two new clinical study protocols for phase 3b trials were filed in June and August (192024-015 and 192024-016, respectively). Comments were received from the Medical Officer on August 25, 2000, concerning the protocol for 192024-016.

On September 18, 2000, NDA 21-275 was received by FDA. Selected files were also submitted to FDA in electronic format over the next week (September 18 through September 26, 2000).

On September 22, 2000, Michael Puglisi of FDA (Project Manager), conveyed a request from Dr. Su Tso, FDA Chemistry Reviewer, to revise the 356h form to include the facility responsible for EtO sterilization. Additionally, revisions to the DMF authorization letters were requested to include details of the filing chronology and location of information. The updated 356h form was submitted to FDA on September 26, 2000. The revised DMF authorization letters were submitted once they became available.

On September 27, 2000, Dr. Tso requested a master index with greater detail than was originally submitted. The updated master index was regenerated and e-mailed to Dr. Tso before the end-of-day. On October 2, 2000, Dr. Tso requested details of the formulations used in the pre-clinical studies, confirmation of the container/closure configurations and labeling used on the stability samples, and requested confirmation of available test data. A response was submitted to FDA on October 10, 2000. This response also included copies of the various e-mails prepared in response to Dr. Tso's requests spanning September 22 through October 2, 2000.

On October 3, 2000, the application was accepted for filing and given a priority review classification by FDA.

On October 24, 2000, Dr. Tso called for the location of the BAK titration-to-failure report and to obtain clarification of the EtO residuals table. The report was located in the Microbiology section of the NDA, so a separate copy of the report was provided on October 26, 2000, along with clarification of the EtO residual table.

On October 27, 2000, Michael Puglisi conveyed a request from the Pharmacology Reviewer for a copy of the complete assay validation and individual subject data for the various pharmacokinetics studies. Additionally, the reviewer requested information on

the stability of the pharmacokinetics samples. The location of these reports within the original NDA and the stability information was provided on November 1, 2000.

On November 28, 2000, an information request was received from Dr. Tso. The request contained 31 questions or requests covering the drug substance, drug product and product labeling. On November 29, 2000, a teleconference with Dr. Tso was held to review each of these requests. A complete response to the majority (27 out of 31) of Dr. Tso's comments was submitted on December 8, 2000. On December 18, 2000, another teleconference was held with Dr. Tso to discuss this response. In the teleconference, Dr. Tso requested additional information to be provided for 4 out of the 27 responses submitted in our December 8, 2000 amendment. On December 29, 2000, a response was provided which addressed all the remaining requests (4 out of the original 31, and 4 out of the 27 responses).

On December 20, 2000, a request from the Pharmacology Reviewer was received through Michael Puglisi to provide details of the formulations used in the pre-clinical studies. Also the reviewer noted that a page was missing from one of the pre-clinical study reports. A response was submitted on December 21, 2000, which included details of the developmental formulations. The missing page of the study report was submitted once it became available (January 4, 2001).

On December 22, 2000, a facsimile was received from Michael Puglisi with a request from the Medical Officer for the location of specific data for study 192024-002. Steve Buxbaum, Director, Allergan Regulatory Affairs, called the Medical Officer to direct him to the location of this data. On December 27, 2000, the Medical Officer requested additional data for study 192024-003. This data was provided to FDA on December 28, 2000. Then on December 29, 2000, the Medical Officer requested the location of specific data for studies 192024-008 and 192024-009. Steve Buxbaum called the Medical Officer to direct him to the location of this data.

On January 3, 2001, a request was received from Zou Chen, Pharmacologist, concerning the safety of the residual solvents, related substances and container/closure extractables found in bimatoprost raw material and/or Lumigan. A detailed response was provided on January 11, 2001.

On January 9, 2001, Zou Chen requested justification of our statement in the labeling regarding exposure multiples. On January 16, 2001, we provided the Pharmacologist with a summary table of information which was included in the original NDA.

On January 16, 2001, a facsimile was received from Michael Puglisi with a request from the Microbiology Reviewer for specific information on the aseptic process for Lumigan. On January 25, 2001, a complete response was submitted to FDA. In a separate document that same day and in accordance with 21 CFR 314.50, the 120-day safety update was submitted to FDA. As part of this update, we submitted proposed labeling changes based upon the updated safety data.

On January 26, 2001, Michael Puglisi sent a facsimile with questions and comments from Dr. Hossein Khorshidi, Reviewing Chemist, and Dr. Tso regarding CMC issues related to bimatoprost and Lumigan. A teleconference was held on January 30, 2001, to obtain clarification and agreement prior to submitting a formal response, which was then sent on February 1, 2001. The revised quality control documents for the test methods were sent as they became available (February 12 and March 1, 2001).

On January 31, 2001, Zhou Chen requested clarification and some additional information regarding our response on January 16, 2001, regarding exposure multiples. Our clarifying response, which included the additional information, was submitted on February 1, 2001. The following day Zhou Chen called Steve Buxbaum and stated that he was unable to locate one of the study reports listed in our response. Later that day the referenced report was identified as incorrect and a copy of the proper report was sent in response.

ASSIGNMENT

WHEREAS we, DAVID F. WOODARD of ORANGE COUNTY, CALIFORNIA, STEVEN W. ANDREWS of ORANGE COUNTY, CALIFORNIA, ROBERT M. BURK of ORANGE COUNTY, CALIFORNIA and MICHAEL E. GARST of ORANGE COUNTY, CALIFORNIA (hereinafter referred to as ASSIGNOR), have invented and own a certain invention entitled: NON-ACIDIC CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS for which application for Letters Patent of the United States was filed on February 22, 1996 under application number 08/605,567.

WHEREAS: ALLERGAN, having its principal place of business at 8301 Mars Drive, Waco, Texas 76712 (hereinafter referred to as ASSIGNEE), is desirous of acquiring the entire interest in, to and under said invention and in, to and under Letters Patent or similar legal protection to be obtained therefor in the United States and in any and all foreign countries.

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that in consideration of the payment by ASSIGNEE TO ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration, ASSIGNOR hereby sells, assigns and transfers to ASSIGNEE the full and exclusive right, title and interest to said invention in the United States and its territorial possessions and in all foreign countries to all Letters Patent or similar legal protection in the United States and its territorial possessions and in any and all foreign countries to be obtained for said invention by said application or any continuation, divisional, renewal, substitute or reissue thereof or any legal equivalent thereof in a foreign country for the full term or terms for which the same may be granted.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and sale;

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said application, said invention and said Letters Patent and legal equivalents in foreign countries as may be known and accessible to ASSIGNOR and will testify as to the same in any interference or litigation related thereto and will promptly execute and deliver to ASSIGNEE or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalent thereof in any foreign country which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this

April 26 th, 19 96

David F. Woodward

State of CALIFORNIA)
) ss:
County of ORANGE)

On 26 April 1996 before me, Tina Sage
personally appeared David F. Woodward
~~personally known to me (or~~ proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

TINA SAGE
COMM. # 1036369
Notary Public — California
ORANGE COUNTY
My Comm. Expires AUG 28, 1998

Notary Public

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this

May 16, 1996.

x Steven W. Andrews
Steven W. Andrews

State of CALIFORNIA)
) ss:
County of ORANGE)

On MAY 16 1996 before me, MARY LOU MCNOWN, a notary public
personally appeared STEVEN W. ANDREWS
~~personally known to me~~ (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

MARY LOU MC NOWN
COMM. # 1059394
Notary Public — California
ORANGE COUNTY
My Comm. Expires AUG 16, 1999

Mary Lou McNown
Notary Public

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this

May 7th, 1996.

Robert M. Burk

Robert M. Burk

State of CALIFORNIA)
) ss:
County of ORANGE)

On MAY 7, 1996 before me, MARY LOU McNOWN, a notary publ.
personally appeared ROBERT M. BURK
personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

MARY LOU MC NOWN
COMM. # 1059394
Notary Public — California
ORANGE COUNTY
My Comm. Expires AUG 16, 1999

Mary Lou McNown
Notary Public

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this

16 May, 1996

Michael E. Garst

Michael E. Garst

State of CALIFORNIA)
) ss:
County of ORANGE)

On MAY 16, 1996 before me, MARY LOU McNOWN, a notary public
personally appeared MICHAEL E. GARST
~~personally known to me~~ (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

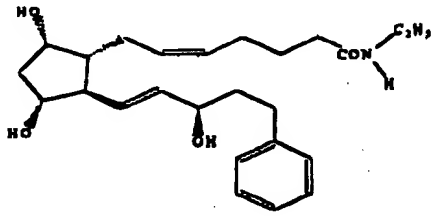
Mary Lou McNown
Notary Public

MARY LOU MC NOWN
COMM. # 1059394
Notary Public — California
ORANGE COUNTY
My Comm. Expires AUG 16, 1999

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03%

DESCRIPTION

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is a synthetic prostamide analog with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is $C_{25}H_{37}NO_4$. Its chemical structure is:



Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. **LUMIGAN™** is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

Each mL contains: Active: bimatoprost 0.3 mg; Preservative: Benzalkonium chloride 0.05 mg; Inactives: Sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bimatoprost is a prostamide, a synthetic structural analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

Pharmacokinetics

Absorption:

After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and were below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing. Mean C_{max} and $AUC_{0\text{-}24hr}$ values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. There was no significant systemic drug accumulation over time.

Distribution
Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism
Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation,
N-deethylation and glucuronidation to form a diverse variety of metabolites.

Elimination
Following an intravenous dose of radiolabeled bimatoprost (3.12 µg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

Clinical Studies:
In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% once daily (in the evening) was 7-8 mmHg.

INDICATIONS AND USAGE

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product.

WARNINGS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% has been reported to cause changes to pigmented tissues. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.

LUMIGAN™ may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has also been reported in association with the use of **LUMIGAN™**.

LUMIGAN™ may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

PRECAUTIONS

General:
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for several months to years (see Warnings). Typically the brown pigmentation around the pupil is expected to spread concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. The increase in brown iris pigment is not expected to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor freckles of the iris are expected to be affected by treatment.

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN™** should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

LUMIGAN™ has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

LUMIGAN™ should not be administered while wearing contact lenses.

LUMIGAN™ has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

Information for Patients:
Patients should be informed that **LUMIGAN™** has been reported to cause increased growth and darkening of eyelashes and darkening of the skin around the eye in some patients. These changes may be permanent.

Some patients may slowly develop darkening of the iris, which may be permanent.

When only one eye is treated, patients should be informed of the potential for a cosmetic difference between the eyes in eyelash length, darkness or thickness, and/or color changes of the eyelid skin or iris.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

Contact lenses should be removed prior to instillation of **LUMIGAN™** and may be reinserted 15 minutes following its administration. Patients should be advised that **LUMIGAN™** contains benzalkonium chloride, which may be absorbed by soft contact lenses.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Carcinogenesis, Mutagenesis, Impairment of fertility:
Carcinogenicity studies were not performed with bimatoprost.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 103 times the recommended human exposure based on blood AUC levels).

Pregnancy: Teratogenic effects: ***Pregnancy Category C.***
In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost, which achieved at least 33, or 97 times, respectively, the intended human exposure based on blood AUC levels.

At doses 41 times the intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN™** administration in pregnant women. Because animal reproductive studies are not always predictive of human response, **LUMIGAN™** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers:
It is not known whether **LUMIGAN™** is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN™** is administered to a nursing woman.

Pediatric use:
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

In clinical trials, the most frequent events associated with the use of **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% occurring in approximately 15% to 45% of patients, in descending order of incidence, included conjunctival hyperemia, growth of eyelashes, and ocular pruritus. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3 to 10% of patients, in descending order of incidence, included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, ocular irritation, and eyelash darkening. The following ocular adverse events reported in approximately 1 to 3% of patients, in descending order of incidence, included: eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 10% of patients were infections (primarily colds and upper respiratory tract infections). The following systemic adverse events reported in approximately 1 to 5% of patients, in descending order of incidence, included headaches, abnormal liver function tests, asthenia and hirsutism.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m^2 is at least 70 times higher than the accidental dose of one bottle of **LUMIGAN™** for a 10 kg child.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 4 hours after the first administration with maximum effect reached within approximately 8 to 12 hours.

LUMIGAN™ may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is supplied sterile in opaque white low density polyethylene ophthalmic dispenser bottles with turquoise polystyrene caps in the following sizes: 2.5 mL fill in 8 mL container – NDC 0023-9187-03, 5mL fill in 8 mL container - NDC 0023-9187-05, or 7.5 mL fill in 8 mL container - NDC 0023-9187-07.

Rx only

Storage: LUMIGAN™ should be stored in the original container at 15° to 25°C (59° to 77°F).

Revised March 2001

Buxbaum_Stephen

From: Michael Puglisi 301-827-2090 FAX 301-827-2531 [PUGLISIM@cder.fda.gov]
Sent: Monday, February 05, 2001 11:55 AM
To: Buxbaum_Stephen
Subject: Re: NDA 21-275: Lumigan tradename

Sensitivity: Confidential

Steve-

The Agency has no objection to the trade name Lumigan. The nomenclature committee (now known as OPDRA- Office of Post-Market Drug Risk Assessment) has recently informed us that they have no objections, and Drs. Chambers and Boyd have also indicated that they have no objections to the name. Let me know if you have any further questions about this matter.

-Mike

>Mike,
>
>A question was asked me this morning at a team meeting: When will we hear
>from the FDA that "Lumigan" is an approved/acceptable name for bimatoprost
>ophthalmic solution? I know you had told me that it would be closer to the
>time of approval that you would check again with the nomenclature committee.
>
>Thanks.
>Steve
>

ALLERGAN PHARMACEUTICALS MEMORANDUM
FDA TELEPHONE CONVERSATIONS

FDA Correspondence

X **Telephone**

Date: October 28, 1998 **IND/NDA:** 48,929

To: S. Buxbaum

From: C. Brissey

Subject: Hypotensive Lipids End of Phase 2 Meeting with the FDA 17 Nov 98

Name of Person(s) Contacted: Raphael Rodriguez

Raphael Rodriguez called to inform us that he must receive the End of Phase 2 Hypotensive Lipids (IND 48,929) briefing packages by Friday, October 30, 1998, or the FDA may need to cancel the November 17, 1998 meeting. Most reviewers will be attending the AAO meeting next week, and it would not be fair to give them only one week to review the package if they did not receive their desk copy until November 9,1998. Some reviewers will want to take the briefing package with them next week for review.

He wants 14 desk copies addressed to his attention, two copies for the Document Room, and the disc that should include the questions to be discussed. He wants to send the questions electronically to the reviewers.

The second alternative for this end of Phase 2 meeting to discuss the CMC section of Hypotensive Lipids could be a teleconference. He is willing to set this up if we decide it is what we want.

NDA 21-275 Correspondence

FDA Correspondence Received	Allergan Application/ Response Sent	Brief Description
N/A	Sep 18, 2000	NDA Submission
Sep 22 thru Oct 2, 2000 (P&F)	Oct 10, 2000	CMC request for additional information and electronic files
Oct 3, 2000 (L)	N/A	NDA accepted by FDA for Priority Review (Note: FDA received application on Sep 18, 2000)
Oct 24, 2000 (P)	Oct 26, 2000	CMC request for additional information or clarification
Oct 27, 2000 (F)	Nov 1, 2000	Pharmacology request for additional information
Nov 28, 2000 (F)	Dec 8, 2000	CMC deficiency comments (Note: majority of responses provided Dec 8, 2000)
Dec 18, 2000 (T)	Dec 29, 2000	CMC comments re: Allergan's Dec 8, 2000 response (Note: response to remaining comments received Nov 28, 2000 and discussion in Dec 18, 2000 teleconference)
Dec 20, 2000 (P)	Dec 21, 2000	Pharmacology request for detail of development formulations used in preclinical studies
Dec 20, 2000 (P)	Jan 4, 2001	Amendment to Pharmacology Study (missing page)
Dec 22, 2000 (F)	Dec 22, 2000 (P)	Medical Officer request for location of data (Note: Reviewer did not require formal response to NDA)
Dec 27, 2000 (F)	Dec 28, 2000	Medical Officer of request for additional data
Dec 29, 2000 (F)	Dec 29, 2000 (P)	Medical Officer request for location of other data (Note: Reviewer did not require formal response to NDA)
Jan 3, 2001 (P&F)	Jan 11, 2001	Pharmacology/Toxicology comments re: drug substance and drug product impurity specifications, and container/closure extractable specifications
Jan 9, 2001 (P)	Jan 16, 2001	Pharmacology/Toxicology comments re: exposure multiples
Jan 16, 2001 (F)	Jan 25, 2001	Microbiology comments – aseptic processing
N/A	Jan 25, 2001	120-Day Safety Update
Jan 26, 2001 (F)	Jan 30, 2001 (T) Feb 1, 2001 Feb 12, 2001	CMC comments re: Allergan's response dated Dec 29, 2000 Detailed response Revised methods
Jan 31, 2001 (P)	Feb 1, 2001	Pharmacology/Toxicology request for clarification of Allergan's response of Jan 16, 2001 re: exposure multiples
Feb 2, 2001 (P)	Feb 2, 2001	Pharmacology/Toxicology request for location of study listed in Allergan's responses re: exposure multiples
Feb 5, 2001 (P)	Feb 5, 2001	New CMC comments
Feb 12, 2001 (F)	Feb 13, 2001 (T)	CMC comments re: Allergan's response dated Feb 1, 2000

P = Phone F = Facsimile L = Letter T = Teleconference E = E-mail M = Meeting

NDA 21-275 Correspondence

FDA Correspondence Received	Allergan Application/ Response Sent	Brief Description
	Feb 16, 2001 (P) Feb 20, 2001	Proposed specifications Detailed response
Feb 13, 2001 (F)	Feb 14, 2001	Labeling – request for expected depletion of inventory
Feb 16, 2001 (E) N/A Feb 28, 2001 (T) Mar 2, 2001 (P) Mar 14, 2001 (P)	Feb 23, 2001 Feb 26, 2001 Mar 1, 2001 Mar 2, 2001 Mar 14, 2001	Labeling – FDA revised package insert Labeling – proposal to remove liver function test statement Labeling – Revised package insert Labeling – Final draft package insert Labeling – Final package insert
Feb 26, 2001 (T)	Feb 26, 2001 Mar 1, 2001	Labeling – 2.5 mL fill size CMC – Extractables table discussed in Feb 13, 2001 t-con CMC – Request for revised methods validation package
Mar 6, 2001 (P)	Mar 6, 2001	Labeling – Slack fill statement on carton
Mar 6, 2001 (P) Mar 13, 2001 (P)	Mar 6, 2001 Mar 20, 2001 March 22, 2001	CMC information re: API for pre-approval inspection Forensic samples shipped Manufacturer information sent
Mar 16, 2001 (L)	N/A	Approval Letter

P = Phone F = Facsimile L = Letter T = Teleconference E = E-mail M = Meeting

FACSIMILE TRANSMISSION
RECORD

From: Su Tso, Ph.D.

Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2539
Fax 301-827-2531

Date: Oct. 2, 2000

To:
Name Steve Buxbaum
Company Allergan Inc.
City Irvine State CA
Phone # (714) 246-4534

FAX # 7140246-4272

Number of Pages (INCLUDING COVER PAGE) 3

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Could not reach you by e-mail yesterday. You may call me for these questions. Let me know what is wrong with the e-mail address.

Su Tso, Ph.D.
Review Chemist, HFD 550
Oct. 2, 2000

Printed by Su Tso

Electronic Mail Message

Date:
From: Su Tso 301-827-2539 FAX 301-827
TSOS@A1
Dept:
Tel No:

Subject: Your e-mail

Steven:

I received your e-mail on the indexing. I also received the CD from Mike, but did not have a change to check the information yet. Thanks

This detailed index for vol. 4 to 9 should be in the original submission under master index.

Please answer the following questions:

1. There should be a section discuss all the formulation used for pre-clinical and clinical studies. If the formulation is the same all the way from beginning of the IND to the NDA submission, please state so. However if there are actually different formulations used, you must discuss the formulation change histroy and include a column "formulation" in the correlation table on pg. 85, vol. 3. In addition, please indicate the phase # (phase II or Phase III) under the column "clinical studies#"

2. Are all the stability data obtained in the final container/closure configuration with or without final label on the bottle.

3. When you will have the 24 month stability data available?

4. we recommended in the pre-NDA meeting that you included the complete testing resuslt of the last time point for the stability of the drug product. But there is no sterility or preservativeness testing data at the 18 months station.

5. Please confirm that the production batch size of the API.

Call me if you do not want to provide these answer by e-mail for confidentiallty.

Su

Su

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-275

OCT - 3 2000

Allergan
Attention: Stephen Buxbaum
Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623

FDA Corresp.
SB
SM
TH
front of NDA

Dear Mr. Buxbaum:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lumigan (bimatoprost ophthalmic solution) 0.03%

Review Priority Classification: Priority (P)

Date of Application: September 18, 2000

Date of Receipt: September 18, 2000

Our Reference Number: NDA 21-275

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 17, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 18, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have requested a waiver as discussed in your Pre-NDA meeting of April 12, 2000.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

Leslie Vaccari
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

FACSIMILE TRANSMISSION RECORD

From: Mike Puglisi, Project Manager

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2522
Fax 301-827-2531

Date October 27, 2000

To:
Name Steve Buxbaum
Company Allergan
City _____ State ____
Phone _____

FAX # 714-246-4272

Number of Pages (INCLUDING COVER PAGE) 1

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Steve - here are a few questions/requests from the Biopharm Reviewer in Regard to Lumigan (NDA 21-275). Please respond in an amendment to your NDA. - Mike

>
>1. The assay validation report summary has been provided by the
> sponsor, but I would like to see the complete assay validation
> report with the actual raw data for the QC samples (eg. inter,
> intra-day accuracy precision,recovery, freeze-thaw stability
> data etc), rather than mean % CVs reported with the current
> submision.
>2. It appears that the long term stability (12 months) of the human
> plasma samples is ongoing. I would like to know how long were
> the human plasma samples stored before they were analyzed for
> the and metabolite content.
>3. The PK studies and in vitro studies are also provided as
> individual study summaries. Only study summaries are not
> acceptable without individual subject data. The sponsor should
> provide detailed reports rather than just reporting mean values.
> Similarly all values should be reported from the therapeutic
> drug monitoring of the Phase III studies rather than reporting
> mean values at Day 0 and Month 3.

NDA-21-275

SA, SM TH 4)

MEMORANDUM

Date: 11/28/00

NDA: 21-275

Between: Steve Buxbaum
Director of Regulatory Affairs
Allergan Inc.
Phone: (714)246-4534
Fax: (714) 246-4272
e-mail: Buxbaum_stephen@Allergan.com

From: Su C. Tso, Ph. D.
Review Chemist
HFD-550
(301) 827-2539 phone
(301) 827-2531 fax
e-mail: Tsos@cder.fda.gov

Date: Nov. 28, 2000

Application #: NDA 21-275

Subject: **Information Request**

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

Drug substance

1. What are the impurity levels of the reference standard # 07-A-243-1 (pg. 174, vol. 2).

2. Add melting point, sulfate ash, and heavy metal to the specifications for Corey aldehyde benzoate (pg. 101, vol. 2).

   What source or sources of starting material will be used in commercial production of bimatoprost

   Provide 2-3 COA for Corey aldehyde benzoate from the source that will be used for the production of bimatoprost drug substance.

3. How is the trans- configuration established and confirmed in intermediate 1, AGN 193957 (pg. 38, vol. 2)?

4. How is the 5,6-cis configuration confirmed in the bimatoprost molecule?

5. In the release analysis and stability report (pg. 229-279 vol. 2), are all the drug substance assay reported as weight % anhydrous basis?

6. Consider improving the resolution between 5,6-trans isomer and the drug substance in HPLC PF-L-029 by condition 2.

Drug product

- Specification:

7. The acceptance criteria for impurity in the specification are reported as %w/w of bimatoprost (pg. 30, vol.3), yet the impurity in analytical method AP-L297 provide calculation (pg. 2, vol. 8) for w/v% and % label claim. Please explain.

8. In the proposed regulatory specification on pg. 30, vol. 3, the individual "unspecified impurity" of 0.5% is not acceptable, it should be 0.1% . The total unspecified impurity may not be necessary.

9. The proposed impurities acceptance criteria for 15-keto, and C1 acid are 0.3% and 0.2% (%w/w) respectively. However these acceptance criteria are above the LOD levels of 0.1% and 0.14% (% label claim), but below the minimum quantitation of 0.38% and 0.57% (% label claim) for 15-keto and C1 Acid respectively. Please clarify the inconsistency or the equivalency of these values.

10. We recommend that you to perform bimatoprost assay by chiral HPLC for the three primary stability batches at the previous or the next time point to show there is no change of configuration at any chiral center.

- Analytical method:

11. Provide data to support the ruggedness for the analytical procedure AP-L127 for BAK.

12. Provide representative CA for the BAK.

- Container/closure:

13. Provide the composition of the ink from Sericol and the composition of the two colorants, PMS 5275 Purple & PMS 326 green (pg. 9 of vol. 7).

14. Which is the correct colorant: PMS 0342 LMB (pg. 7, vol. 7) or PMS 03421 LMB (pg. 20, 23, 24, vol. 3)?

15. Has the turquoise concentrate HIPs (pg. 8, vol. 7) been used in any marketed product?

16. In the phase I cap extractable study (pg. 223, vol. 7), how is the 70.6 ug/cap or 8 ppb/formulation calculated? Was a similar peak (by HPLC AP-ID073 method with retention time 6.45 min.) observed by the same method in the stability study for extractable on pg. 307, vol. 9?

17. An extractable was detected at retention time of 7 min. (pg. 285, vol. 7) with the labeled sample by the HPLC gradient method AP-ID073 in the label probe study. Is this the same peak that was observed in question 16? Did you use HPLC method AP-ID073 to check the presence of this peak in your primary stability lot (pg. 307, vol. 9)? What is the max. level detected?

18. The two extractables were detected with retention times at 2.4 and 2.8 min. by AP-L297 on pg. 282, vol. 7. Did you confirm the presence or absence of these two peaks in the stability study on pg. 307, vol. 9?

19. Discuss the 17 min. peak by the GC method on pg. 275 and 283, vol. 7

20. How is the daily dose of 0.17 ug/day calculated for the 4 min. peak detected by GC method (pg. 310 and 320, vol. 9)? Please explain.

21. Where is the GC peak at 12 min. on Pg. 338, vol. 9? What is the max. level observed? Please explain data on pg. 124-128, vol. 9. How does the 12 min. peak relate to the 17 min. peak detected on pg. 275 and 283 by the same GC method?

22. There are three extractables found by the HPLC BAK method AP-L127 in the stability study on pg. 307, vol. 9. How low is the level of the third HPLC peak found? What are the max. levels observed for each of these peaks in the stability study (specify time point)?, What is the total daily dose for the BAK HPLC extractables (pg. 318-319, vol. 9).

- Stability:

23. Provide the 18 month test results for particualte matter and sterility if the 24 months stability data are not available soon.

24. Confirm that the 3 mL fill in 8 mL container is a professional sample?

25. Provide data of all extractables by BAK method AP-L127 at each stability time point to see their change with time (see question # 22).

26. Please explain 5E & 024ORS in the Table on pg. 276, 279, vol. 9. Impurities other than 15-beta isomer are not reported in the photo-studies. From the data presented, it is shown that the drug substance is sensitive to light, therefore, the statement on pg. 272, vol. 9, last sentence of 2nd paragraph is inconsistent with the data, please explain!

27. Provide HPLC chromatograms (initial and the latest stability time point) for each of the three primary stability batches.

28. For the container/closure components sterilization, please confirm the total aeration time and conditions before they can be used for the filling operation.

29. In the stability protocol (pg. 205, vol. 4), for the sampling procedure after the words of "these initial batches", please add "at least" before the words " one batch of each fill size-----"

- Labeling

30. Package insert:

Under DESCRIPTION: Add molecular weight for bimatoprost, and add pH for bimatoprost ophthalmic solution.

Under HOW SUPPLIED section: Change "plastic" to "white LDPE"

Bottle and carton labels:

For the 3 ml container, the word of " professional" should be added before the word of "sample".

Add INDICATION to all container sizes.

Add the address of Allergan Inc.

31. Provide mock-up samples of immediate container label and carton label. These should be provided before approval of the NDA.

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Steve Buxbaum	**From:** Mike Puglisi
Fax: 714-246-4272	**Fax:** 301-827-2531
Phone:	**Phone:** 301-827-2522
Pages: 2 (incl. cover)	**Date:** December 22, 2000

Re: Medical Officer's comments re: NDA 21-275

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Steve-

Here's a request from our Medical Officer regarding NDA 21-275 (Lumigan). Please address this issue in an amendment to the NDA. Feel free to call me if you have any questions.

-Mike

NDA 21-275
Lumigan

Medical Officer's Request for Additional Information **December 22, 2000**

Regarding Protocol 192024-002:

In the Appendices, Section E1, Mean IOP at Each Timepoint [paper NDA Volume 58, page 381], the values for the 4PM timepoints on Days 14, 21, and 28 are missing.

Can you provide the location of these mean IOPs or direct me to their location in the NDA? Thanks.

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

SB
SM
TH
file

To: Steve Buxbaum	**From:** Mike Puglisi
Fax: 714-246-4272	**Fax:** 301-827-2531
Phone:	**Phone:** 301-827-2522
Pages: 2 (incl. cover)	**Date:** December 27, 2000
Re: Medical Officer's comments re: NDA 21-275	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Steve-

Here's another request from our Medical Officer regarding NDA 21-275 (Lumigan). Please address this issue in an amendment to the NDA. Feel free to call me if you have any questions.

-Mike

NDA 21-275
Lumigan

Medical Officer's Request for Additional Information **December 27, 2000**

Regarding Protocol 192024-003, Volume 59:

I am unable to locate the mean IOPs (not mean changes from baseline) for the timepoints measured on Days 1, 14, 28, and 29.

Can you provide these mean IOPs or direct me to their location in the NDA? Thanks.

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Steve Buxbaum	**From:** Mike Puglisi
Fax: 714-248-4272	**Fax:** 301-827-2531
Phone:	**Phone:** 301-827-2522
Pages: 2 (Incl. cover)	**Date:** December 29, 2000

Re: Medical Officer's comments re: NDA 21-275

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Steve-

Here's another request from our Medical Officer regarding NDA 21-275 (Lumigan). Please address this issue in an amendment to the NDA. Feel free to call me if you have any questions.

-Mike

NDA 21-275
Lumigan

Medical Officer's Request for Additional Information **December 29, 2000**

Regarding Protocols 192024-008 and –009:

At selected centers, corneal pachymetry measurements were to be performed on Day 0 after the visual field and IOP exams.

Can you specify the location of these measurements in the NDA or provide these measurements? Thanks.

FACSIMILE TRANSMISSION RECORD

From: **Mike Puglisi, Project Manager**

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2522
Fax 301-827-2531

Date 1/3/01

To:
Name Steve Burbaum
Company Allergan
City _____ State ____
Phone _____

FAX # 714-246-4272

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Steve - Here's that list of Impurities we discussed earlier today. Please call me if you have any questions Re: the issue.

Thanks,

Mike

Drug substance specification:

Residual solvents:

Ethyl acetate	0.2%
Heptanes	0.2%

Related substances:

15-keto isomer	NMT 0.2% (w/w)
5,6-trans isomer	NMT 0.5%
15-β isomer	NMT 0.8%
C1 acid	NMT 0.1%
Triophenylphosphine oxide	NMT 0.1%

Drug product specification:

15-keto isomer	NMT 0.3% (w/w)
15-β isomer	NMT 0.9%
C1 acid	NMT 0.2%

Container/closure extractables:

Three extractables were observed by HPLC method and two by GC method.

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Steve Buxbaum	**From:** Mike Puglisi
Fax: 714-246-4272	**Fax:** 301-827-2531
Phone:	**Phone:** 301-827-2522
Pages: 4(incl. cover)	**Date:** January 16, 2001

Re: Microbiologist deficiencies and comments re: NDA 21-275 (Lumigan)

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Steve-

Here are the Microbiologist's comments re: the Lumigan NDA. Please respond in an Amendment to your NDA. Feel free to call me if you have any questions.

-Mike

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NDA 21-275

January 16, 2001

List of Microbial Deficiencies and Comments

A. Microbiology Deficiencies:

1. Please provide the following facility and environmental control information:

   a. The air pressure differentials and room classifications for the areas shown in the personnel flow map on p. 308 of vol. 49

   b. A description of the WFI system

2. Please address the following issues regarding the filling process:

   a. On pages 8 and 9 of vol. 49, the applicant states that "The main batch vessel containing the finished bulk product is transported to the product transfer room. Using a positive displacement pump, the sterile bulk product is transferred on demand from the main batch vessel through the sterilizing filter to the filling machine and filled into the pre-sterilized container-closure system." Where is the product transfer room located and what is its room classification?

   b. When is the product transferred to the intermediate surge container during this process?

   c. Please describe exactly what happens to the bulk drug product from compounding to filling. Be sure to include all equipment used, transport of the drug product between rooms, and transfer of the drug product through the sterilizing filter and between equipment. A diagram of product flow through the facility and the compounding/filling process might be useful.

   d. Please provide the hold times between the compounding, filtration, and filling processes.

   e. How and where are the containers capped?

3. Please address the following environmental monitoring issues:

   a. The applicant should provide the environmental monitoring alert and action limits for each sampling method and each area tested.

   b. The locations of air, surface, and personnel monitoring should be provided.

c. Is the bulk solution bioburden determined for the aqueous drug product prior to filtration? Also, provide detailed information regarding the location, duration, and methods of bulk material storage from the time of microbial limits testing until compounding.

d. A more detailed description of the actions taken when alert and action limits are exceeded should be provided.

4. Please address the following issues regarding container/closure sterilization:

a. Does the validation load represent the "worst case" load? Is this the only load pattern to be used for the sterilization of bottles and caps?

b. How are the sterilized containers packaged for sterile transport to the filling room of the drug manufacturing facility?

c. How long are the containers and closures aerated prior to packaging?

5. Please address the following issues regarding components and in-process sterilization:

a. The applicant should explain why biological indicators were not used in the validation of the steam-in-place procedure.

b. The applicant should provide a diagram of the steam-in-place system. Depending on the size and orientation of the steam-in-place system, additional monitoring sites may be warranted.

c. Where were the biological indicator spore counts determined?

6. Please address the following issues regarding process validations:

a. Please provide a more detailed description of the environmental monitoring process for media fills (including the sites, frequency, methods of testing, and alert and action limits) and the results of environmental monitoring from media fills 6220, 6221 and 6456.

b. It is not clear which filter will be used for production batches of drug product. On p. 9 of vol. 49, the applicant states that the drug product "is filtered through a 5-inch 0.2 um sterilizing grade filter (Pall Suporflow SCS92SP75) into a sterile 45-L glass surge vessel." And on page 157 it says that the filter used for the commercial scale process is the SCS92SP71S 10" filter cartridge.

c. How many times are the sterilizing filters autoclaved and re-used? Is the integrity of the sterilizing filter confirmed following each use?

d. Integrity testing should be done on the same container/closure system used to package Lumigan. How do the "Sophia" bottles and caps referenced on p. 313 of vol. 50 differ from the 8 mL Boston Round bottles and caps referenced on p. 12 of vol. 49?

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. A contamination limit of 1 in 1000 for media fills (p. 307) implies that up to 5 contaminated vials out of 5000 vials filled during each run is acceptable. If this is the case, the applicant should consider changing the media fill acceptance criteria.

FACSIMILE TRANSMISSION RECORD

From: HOSSEIN S. KHORSHIDI, Ph.D.

Division of Anti-Inflamm
and Ophthalmic Drug Pr

Phone 301-827-
Fax 301-827-

Date: 1/26/01

To:

Name Stephen Buxbaum, Director, Regulatory Affairs

Company Allergan

City Irvine State CA

Phone # (714) 246-4534

FAX # (714) 246-4272

Number of Pages (INCLUDING COVER PAGE) ____

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is

Additional message:

January 26, 2001

NDA 21-275

Lumigan™ (bimatoprost) Ophthalmic Solution, 0.03%

CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

Drug Substance:

1. Specify a range (as acceptance criteria) for melting point and optical rotation tests in the specification for the starting material, Corey Aldehyde Benzoate (CAB).

Drug Product:

2. In your response to question No. 21.b, you have mentioned "method *AP-ID-073 as a GC method*" while the same method has been referenced as HPLC in other places (e.g., your response to questions # 16 and 17 of amendment dated 12/8/00). Please clarify this inconsistency.

3. The following impurities with proposed acceptance criteria should be included in the drug product specification at release and stability.

Retention time	Method	Proposed acceptance criteria
2.4 min	HPLC	NMT 0.2%
2.8 min	HPLC	NMT 0.2%
3.6 min	HPLC	NMT 0.2%
4.5 min	HPLC	NMT 0.2%
5.5 min	HPLC	NMT 0.2%

Moreover, in the listing of the impurities in the analytical procedure, state the source of the impurities (e.g., degradation products or extractables).

4. Is the ETO residuals testing performed regularly for release of the sterilized container/closure components according to SOP TS-015D?

5. Submit the revised drug substance and drug product specification sheets.

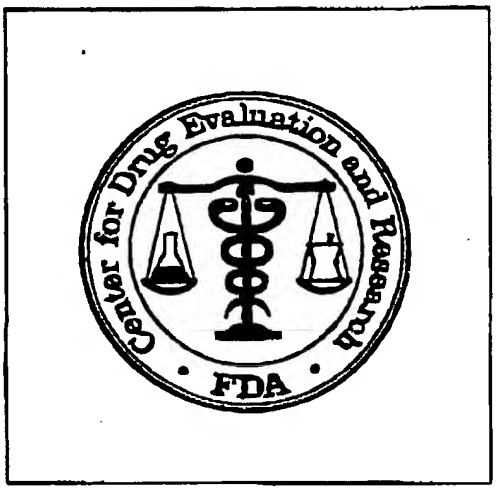
6. Submit the method validation packages (including all revised methods, e.g. HPLC method AP-L297) in three copies once the issue in question No. 3 is resolved.

Labeling:

7. Is the provided mock up presentation (for the immediate containers) the true and actual size or they have been enlarged?

8 In the bottle and carton labels for the 3 ml and 5 ml fill, you have stated "bottles filled to approximately 1/2 capacity for proper drop control." Such statement is absent in labels for the 7.5 ml fill. Please explain.

FACSIMILE TRANSMISSION RECORD



From: Hossein S. Khorshidi

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

Phone 301-827-2040
Fax 301-827-2531

Date: 2/12/01

To:

Name Stephen Buxbaum, Director, Regulatory Affairs
Company Allergan
City Irvine State CA
Phone # ~~(714) 246-4534~~
FAX # (714) 246-4272

Number of Pages (INCLUDING COVER PAGE) ____

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

Additional message:

Feburary 12, 2001

NDA 21-275

Lumigan™ (bimatoprost) Ophthalmic Solution, 0.03%

CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

Extractable:

1. Provide adequate toxicological/risk assessment data for the 5.5 min peak (detected by BAK HPLC, method AP-L127), 2.4, 2.8 min peaks (detected by impurities HPLC, method AP-L 297) and 4.0 min peak (detected by GC, method AP-G063-2). In the absence of such toxicological data, and for quality assurance purpose, the following acceptance criteria are proposed:

Peak at 5.5 min (BAK HPLC method, AP-L127):	NMT 0.5%
Peak at 2.4 min (Impurity HPLC method, AP-L 297):	NMT 0.2%
Peak at 2.8 min (Impurity HPLC method, AP-L 297):	NMT 0.2%
Peak at 4.0 min (GC method, AP-G063-2):	< 1.0%

The 3.6 min and 4.5 min peaks can be reported without acceptance criteria.

These peaks should be listed under separate entry as "extractable impurities" in drug product specification. Moreover, it is recommended that the observed level of extractables be reported as % w/w to active drug substance present in drug product.

2. In general, acceptance criteria for the extractable impurities can be omitted if adequate toxicological/risk assessment data are provided.

3. Footnote "a" in drug product specification should read as "exclude only process impurities from Bimatoprost synthesis".

4. Please comment on the peak observed at 7.7 min (by gradient HPLC, method AP-ID073). Is there any relationship between this peak and those observed by the above mentioned HPLC and GC methods?

5. Submit the revised drug product specification once all issues regarding extractables are resolved.

Labeling:

6. To increase the legibility of the immediate container, the following revision should be made:

a. Eliminate the statement *"Bottle filled to approximately 1/2 capacity for proper drop control"* wherever applicable.

b. The statement *"Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8 -7.8."* should be replaced with "Sodium hydroxide and/or hydrochloric acid may be added to adjust pH (6.8 -7.8).

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Steve Buxbaum	**From:** Mike Puglisi
Fax: 714-246-4272	**Fax:** 301-827-2531
Phone:	**Phone:** 301-827-2522
Pages: 2(incl. cover)	**Date:** February 13, 2001
Re: Container labeling for Lumigan (NDA 21-275)	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Steve-

We understand that container and/or carton labeling for Lumigan has already been printed. Attached are some questions from Dr. Chambers re: that labeling. Please call me if you have any questions about this matter.

-Mike

NDA 21-275

February 13, 2001

Questions to the sponsor:

1. How much labeling was printed?
2. How long is it expected to last?
3. When is the next scheduled printing?
4. When was the current supply printed?
5. Why was it printed without the Agency's input?

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Steve Buxbaum	**From:** Mike Puglisi
Fax: 714-248-4272	**Fax:** 301-827-2531
Phone:	**Phone:** 301-827-2522
Pages: 7(incl. cover)	**Date:** February 28, 2001

Re: Agency revised package insert for Lumigan (NDA 21-275)

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Steve-

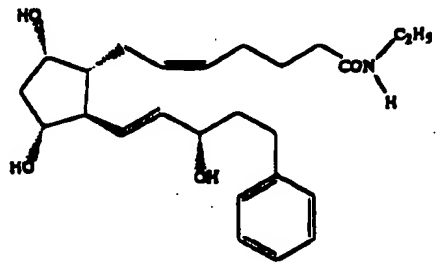
Here's our revised package insert for Lumigan, as of 2/28/01. Please examine carefully – there have been changes to the document.

-Mike

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03%

DESCRIPTION

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is a synthetic prostamide analog with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is $C_{25}H_{37}NO_4$. Its chemical structure is:



Good Acceptable D

Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. **LUMIGAN™** is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

Each mL contains: Active: bimatoprost 0.3 mg; Preservative: Benzalkonium chloride 0.05 mg; Inactives: Sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bimatoprost is a prostamide, a synthetic analog of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

Pharmacokinetics

Absorption:

After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and were below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing. Mean C_{max} and $AUC_{0\text{-}24hr}$ values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. There was no significant systemic drug accumulation over time.

Distribution
Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism
Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-dethylation, and glucuronidation to form a diverse variety of metabolites.

Elimination
Following an intravenous dose of radiolabeled bimatoprost (3.12 µg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

Clinical Studies:
In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% once daily (in the evening) was 7-8 mmHg.

INDICATIONS AND USAGE

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product.

WARNINGS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.

LUMIGAN™ may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has also been reported in association with the use of **LUMIGAN™**.

LUMIGAN™ may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes. copy addition

PRECAUTIONS

General:

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for Patients).

New Add'l

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for several months to years (see Warnings). Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor freckles of the iris have been affected by treatment.

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis).

Macular edema, including cystoid macular edema, has been reported rarely during treatment with bimatoprost ophthalmic solution. LUMIGAN™ should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

LUMIGAN™ has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

LUMIGAN™ should not be administered while wearing contact lenses.

LUMIGAN™ has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

Information for Patients:
Patients should be informed that **LUMIGAN™** has been reported to cause increased growth and darkening of eyelashes and darkening of the skin around the eye in some patients. These changes may be permanent.

Some patients may slowly develop darkening of the iris, which may be permanent.

When only one eye is treated, patients should be informed of the potential for a cosmetic difference between the eyes in eyelash length, darkness or thickness, and/or color changes of the eyelid skin or iris.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

Contact lenses should be removed prior to instillation of **LUMIGAN™** and may be reinserted 15 minutes following its administration. Patients should be advised that **LUMIGAN™** contains benzalkonium chloride, which may be absorbed by soft contact lenses.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Carcinogenesis, Mutagenesis, Impairment of fertility:
Carcinogenicity studies were not performed with bimatoprost.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 103 times the recommended human exposure based on blood AUC levels).

Pregnancy: Teratogenic effects: ***Pregnancy Category C:***
In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the intended human exposure based on blood AUC levels.

Maternal toxicity, evidenced by reduced gestation length, late resorptions, fetal death, postnatal mortality and reduced pup body weights were observed when female rats received oral doses which achieved at least 41 times the intended human exposure based on blood AUC levels.

There are no adequate and well-controlled studies of **LUMIGAN™** administration in pregnant women. Because animal reproductive studies are not always predictive of human response, **LUMIGAN™** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers:
It is not known whether **LUMIGAN™** is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN™** is administered to a nursing woman.

Pediatric use:
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

In clinical trials, the most frequent event associated with the use of **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% has been conjunctival hyperemia (45%). Growth of eyelashes has been reported in approximately 40% of patients, and ocular pruritus has been reported in approximately 15% of patients. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3 to 10% of patients included blepharitis, cataract, eye pain, eyelash darkening, eyelid erythema, foreign body sensation, ocular burning, ocular dryness, ocular irritation, pigmentation of the periocular skin, superficial punctate keratitis, and visual disturbance. The following ocular adverse events were reported in approximately 1 to 3% of patients: allergic conjunctivitis, asthenopia, conjunctival edema, eye discharge, increases in iris pigmentation, photophobia, and tearing. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 1-5% of patients included abnormal liver function tests, asthenia, headaches, hirsutism, and infections (primarily colds and upper respiratory tract infections).

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% occurs, treatment should be symptomatic.

In 2-week oral (by gavage) mouse and rat studies, doses up to 250 mg/kg/day did not produce any toxicity. This dose expressed as mg/kg is 2,700 times higher than the accidental dose of one bottle of LUMIGAN™ for a 10 kg child.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 4 hours after the first administration with maximum effect reached within approximately 8 to 12 hours.

Moved to Clin 4.7-d.1/2

LUMIGAN™ may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is supplied sterile in opaque white low density polyethylene ophthalmic dispenser bottles with turquoise polystyrene caps in the following sizes: 2.5 mL fill in 8 mL container – NDC 0023-9187-03, 5 mL fill in 8 mL container – NDC 0023-9187-05, or 7.5 mL fill in 8 mL container - NDC 0023-9187-07.

Rx only

Storage: LUMIGAN™ should be stored in the original container at 15° to 25°C (59° to 77°F).

Revised February 2001

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-275

Allergan, Incorporated
Attention: Stephen Buxbaum
Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623-9534

Dear Mr. Buxbaum:

Please refer to your new drug application (NDA) dated September 18, 2000, received September 18, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lumigan (bimatoprost ophthalmic solution) 0.03% .

We acknowledge receipt of your submissions dated October 10 and 26, November 1, and December 8, 21, 22, 28, and 29, 2000; and January 4, 16, 23, and 25, February 1 (two), 2, 5, 12, 14, 20, 23, and 26 (two), and March 1 (two), 2, 5, and 14, 2001.

This new drug application provides for the use of Lumigan (bimatoprost ophthalmic solution) for reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) of the package insert must be identical to the attached draft labeling submitted March 14, 2001. The immediate container and carton labels must be identical in content to the labeling of the package insert. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-275." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

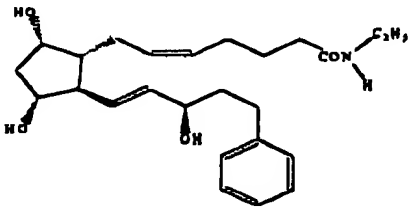
{See appended electronic signature page}

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03%

DESCRIPTION

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is a synthetic prostamide analog with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is $C_{25}H_{37}NO_4$. Its chemical structure is:



Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. **LUMIGAN™** is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

Each mL contains: Active: bimatoprost 0.3 mg; Preservative: Benzalkonium chloride 0.05 mg; Inactives: Sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bimatoprost is a prostamide, a synthetic structural analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

Pharmacokinetics

Absorption:

After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and were below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing. Mean C_{max} and $AUC_{0\text{-}24hr}$ values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. There was no significant systemic drug accumulation over time.

Distribution
Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism
Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation,
N-deethylation and glucuronidation to form a diverse variety of metabolites.

Elimination
Following an intravenous dose of radiolabeled bimatoprost (3.12 µg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

Clinical Studies:
In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% once daily (in the evening) was 7-8 mmHg.

INDICATIONS AND USAGE

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product.

WARNINGS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% has been reported to cause changes to pigmented tissues. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.

LUMIGAN™ may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Distribution
Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism
Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation,
N-deethylation and glucuronidation to form a diverse variety of metabolites.

Elimination
Following an intravenous dose of radiolabeled bimatoprost (3.12 µg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

Clinical Studies:
In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% once daily (in the evening) was 7-8 mmHg.

INDICATIONS AND USAGE

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product.

WARNINGS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% has been reported to cause changes to pigmented tissues. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.

LUMIGAN™ may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Distribution
Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism
Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation,
N-deethylation and glucuronidation to form a diverse variety of metabolites.

Elimination
Following an intravenous dose of radiolabeled bimatoprost (3.12 μg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

Clinical Studies:
In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% once daily (in the evening) was 7-8 mmHg.

INDICATIONS AND USAGE

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product.

WARNINGS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% has been reported to cause changes to pigmented tissues. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.

LUMIGAN™ may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has also been reported in association with the use of **LUMIGAN™**.

LUMIGAN™ may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

PRECAUTIONS

General:

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for several months to years (see Warnings). Typically the brown pigmentation around the pupil is expected to spread concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. The increase in brown iris pigment is not expected to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor freckles of the iris are expected to be affected by treatment.

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN™** should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

LUMIGAN™ has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

LUMIGAN™ should not be administered while wearing contact lenses.

LUMIGAN™ has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

Information for Patients:
Patients should be informed that **LUMIGAN™** has been reported to cause increased growth and darkening of eyelashes and darkening of the skin around the eye in some patients. These changes may be permanent.

Some patients may slowly develop darkening of the iris, which may be permanent.

When only one eye is treated, patients should be informed of the potential for a cosmetic difference between the eyes in eyelash length, darkness or thickness, and/or color changes of the eyelid skin or iris.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

Contact lenses should be removed prior to instillation of **LUMIGAN™** and may be reinserted 15 minutes following its administration. Patients should be advised that **LUMIGAN™** contains benzalkonium chloride, which may be absorbed by soft contact lenses.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Carcinogenesis, Mutagenesis, Impairment of fertility:
Carcinogenicity studies were not performed with bimatoprost.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 103 times the recommended human exposure based on blood AUC levels).

Pregnancy: Teratogenic effects: ***Pregnancy Category C.***
In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost, which achieved at least 33, or 97 times, respectively, the intended human exposure based on blood AUC levels.

At doses 41 times the intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN™** administration in pregnant women. Because animal reproductive studies are not always predictive of human response, **LUMIGAN™** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers:
It is not known whether **LUMIGAN™** is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN™** is administered to a nursing woman.

Pediatric use:
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

In clinical trials, the most frequent events associated with the use of **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% occurring in approximately 15% to 45% of patients, in descending order of incidence, included conjunctival hyperemia, growth of eyelashes, and ocular pruritus. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3 to 10% of patients, in descending order of incidence, included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, ocular irritation, and eyelash darkening. The following ocular adverse events reported in approximately 1 to 3% of patients, in descending order of incidence, included: eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 10% of patients were infections (primarily colds and upper respiratory tract infections). The following systemic adverse events reported in approximately 1 to 5% of patients, in descending order of incidence, included headaches, abnormal liver function tests, asthenia and hirsutism.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m^2 is at least 70 times higher than the accidental dose of one bottle of **LUMIGAN™** for a 10 kg child.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 4 hours after the first administration with maximum effect reached within approximately 8 to 12 hours.

LUMIGAN™ may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is supplied sterile in opaque white low density polyethylene ophthalmic dispenser bottles with turquoise polystyrene caps in the following sizes: 2.5 mL fill in 8 mL container – NDC 0023-9187-03, 5mL fill in 8 mL container - NDC 0023-9187-05, or 7.5 mL fill in 8 mL container - NDC 0023-9187-07.

Rx only

Storage: LUMIGAN™ should be stored in the original container at 15° to 25°C (59° to 77°F).

Revised March 2001

/s/

Robert DeLap
3/16/01 07:05:20 AM